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PATHOGENESIS OF RHEUMATIC FEVER*

By WM. J. KERR, M.D., F.A.C.P., *San Francisco, California*

RHEUMATIC fever is one of our most serious diseases. It attacks children primarily but under conditions of crowding, exposure, and fatigue, may affect older age groups in certain localities as was demonstrated in the recent war. The late manifestations of the disease are so disabling that they produce our most serious medical economic and social problems in the prime of life for those so afflicted.

There is abundant evidence that microörganisms of the *streptococcus group* are the etiological agents which initiate a train of reactions in the host resulting in the lesions characteristic of the disease. It is not proved that a single strain of streptococci is the specific agent, although beta-hemolytic streptococci of one or more specific types are generally isolated from the throat of patients early in the course of the disease in different outbreaks. The many points of similarity to the pathogenesis of scarlet fever, where certain strains of beta-hemolytic streptococcus are almost undeniably the etiological agents, support the view that types of streptococci initiate the immunological mechanisms in rheumatic fever. The appearance and fluctuations in specific streptolysin titers in patients appears also to be of significance, although this and other immunity reactions may appear in persons who show no clinical evidence of the localizations of rheumatic fever in the tissues. A significant difference between rheumatic fever and scarlet fever lies in the frequency with which pyogenic lesions appear in the latter in the lymphatic tissues and throughout the body. The streptococci in scarlet fever appear to provoke not only a more violent general reaction with outward manifestations in the skin and lymph nodes, but also more evidence of invasion by the organisms than is generally observed in rheumatic fever.

The *seasonal occurrence of outbreaks* of rheumatic fever at the time of year when streptococcal infections are prevalent lends further support to the

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view that these organisms are etiological factors. It is apparent from observations made in military installations during the recent war that certain localities show a higher attack rate for rheumatic fever than others under conditions of congregation, housing, clothing, physical activity and dietary habits, which are common to all similar installations. While inclement weather (more often experienced in temperate climates) may be an important factor, it would appear that the conditions favorable for the beta-hemolyticus streptococcus are of determining significance.

The *rôle of under nutrition* in general, and of the accessory dietary factors in particular, is difficult to evaluate. In civil life the high prevalence of rheumatic fever among those in the lower economic brackets may indicate only generally lowered resistance to infection. There is evidence that a deficiency of accessory dietary factors is widespread in this economic group. The tendency to purpuric manifestations appears to be high at the season when rheumatic fever is prevalent, and vitamin C content of the blood at such times is generally low. The hemorrhagic tendency is a feature of the symptom complex of rheumatic fever and may be readily controlled by supplemental intake of this vitamin. Although it must be assumed that general nutrition is inadequate, and that other factors than vitamin C may be of importance, it is possible that the vascular integrity of those attacked is faulty, thus rendering tissues vulnerable to injury.

The *portal of entry* is generally assumed to be the upper respiratory tract, although if the streptococcus is the etiological agent, we must assume that any site where the organisms gain a foothold may serve as a portal. There is scant evidence that the streptococcus actually spreads beyond the pharyngeal wall, the tonsils, and other local lymphatic structures, or at times, the peritonsillar tissues. The occasional demonstration of streptococci in synovial fluids and elsewhere in body fluids, and tissues in patients with rheumatic fever and many other diseases, is not surprising in view of the ubiquitous nature and varying pathogenicity of these organisms. The almost constant failure to find the same type specific streptococci in the throat and in the tissues generally involved suggests that the reactions throughout the body are in response to substances produced locally in the pharynx, and acting through humoral mechanisms on distant tissues. If the substance produced locally is cytotoxic, it is obvious that it differs somewhat from the toxic material responsible for the more violent systemic reactions and the dermatological responses in scarlet fever.

The *silent period* of some days to two or three weeks following the pharyngeal symptoms is one of the striking and characteristic features of rheumatic fever. A similar pause is observed in scarlet fever before the renal, articular and cardiac manifestations appear. It is during this period that immune mechanisms are set in motion. An increased antistreptolysin titer is almost constantly observed.

The *clinical manifestations* of varying severity then make their appearance in the synovial membranes and other connective tissues, in the cardiac

valves, myocardium and pericardium, in the skin, brain, lungs, and kidneys, with symptoms and signs peculiar to the organs and structures concerned. Other involvements are more subtle, seldom causing revealing symptoms and signs, but it is apparent from cytological studies that lesions are widespread and bear an intimate relationship to the vascular and perivascular structures. The systemic symptoms including fever, leukocytosis and rapid sedimentation of red blood cells are not peculiar to rheumatic fever but common to many infectious diseases.

The *course* of rheumatic fever is variable. There is a tendency to chronicity and seasonal recurrence and during recurrent attacks the pattern of symptoms and signs in a given patient is not always repeated. In fact, over a period of years, episodes of reactivity in the cardiac structures particularly may appear without systemic symptoms of an infection, or other symptoms in the joints, or elsewhere. A small percentage of persons with advanced valvular disease of rheumatic origin may have had no history of preceding illness resembling rheumatic fever. Many patients with rheumatic cardiac disease of long standing, who present themselves with myocardial failure and abnormal mechanisms, will show at necropsy histological evidence of rheumatic activity.

The *lesions* of rheumatic fever are of microscopic size and diffusely located in relation to smaller blood vessels. It is held by many that the lesions are as specific for rheumatic fever as the tubercle is specific for tuberculosis. It is obvious that neither assumption is correct. However, the Aschoff body when found in the tissues of a patient with other evidence of rheumatic disease supports the diagnosis, but we must consider other types of vascular disease which clinically differ from rheumatic fever, e.g., lupus erythematosis disseminata, and periarteritis nodosa particularly. The reactions in the synovial membranes, subcutaneous tissues, cardiac valves, cardiac muscle, pericardium, lungs and brain, differ in the degree of exudation so markedly that in some tissues the cellular components are not arranged in the compact masses which are seen so characteristically in the myocardium. The tissue reaction occurs as a small necrotic area around the small blood vessels and is made up of polymorphonuclear leukocytes and cells with a large basophilic cytoplasm. The latter cells are often multinuclear. There is a localized increase in vascularity. As the lesion progresses plasma cells and fibroblasts appear, gradually replacing the basophilic cells. The end-result is a small area of fibrosis. The only tissues where lesions cause damage of a permanent, progressive and crippling nature are in the heart. Why the proliferative features of the process assume such significance in the heart is unknown. The organization of the lesions in the valves and pericardium leads to mechanical disturbances which affect hemodynamics and lead to myocardial failure. The joints are seldom affected permanently. The kidneys may suffer chronic and progressive injury.

The *treatment* of rheumatic fever is generally unsatisfactory. The studies of Chandler and Taussig suggests that continuous or seasonal use

of small daily oral doses of the sulfonamide drugs may prevent recurrences or first attacks by reducing the attack rate of hemolytic streptococcus infection. Removal of the tonsils may prevent initial attacks of rheumatic fever but this procedure apparently has no effect in preventing recurrences. Removal to a warmer and more equable climate may be beneficial in preventing recurrences, chiefly, it would appear, from the chance it offers of escape from streptococcal exposure. The salicylate drugs are useful in controlling the systemic reactions and in reducing the symptoms and signs related to the exudative process, but there is little evidence that the over-all course of the disease or the end-results are altered by this or any other drug now available. The heroic use of antibiotics and salicylates during the recent war did not result in a cure of the process in the tissues. Other methods of active treatment have also been found wanting. It is probable that once the "trap is set" by the streptococcus in the pharynx, the train of events progresses by some immunological process which originates in the host and which cannot be interrupted by any therapeutic method yet devised.

The *immunological processes* which are involved in rheumatic fever and scarlet fever are not completely understood. There are, however, some clues which, when assembled, shed some light on the problem and point the way for future study. Swift suggested that the synovial membranes and other tissues were sensitized during the silent period following the initial infection and then reacted somewhat like tissues respond after an injection of foreign protein (horse serum). Recent experimental studies by Rich and Gregory indicate that lesions resembling those in rheumatic carditis can result from anaphylactic hypersensitivity. More recent studies by Rich and clinical experience suggest that sensitization to the sulfonamides may cause widespread vascular lesions resembling those seen in periarteritis nodosa, lupus erythematosis, and rheumatic arteritis. Numerous workers have attempted to produce rheumatic fever and glomerulonephritis by repeated injections of streptococci or their products and other antigens and toxins, as well as foreign proteins including foreign serums. The lesions produced by foreign serum in rabbits may bear some resemblance to those of rheumatic fever. In experimental glomerulonephritis the most consistent results have been obtained by the use of specific antikidney serum. Masugi and others have demonstrated that chronic glomerulonephritis with its major clinical and pathological features can be produced by this method. The nephritis appears to be the direct result of the antigen-antibody reaction caused by the interaction of the antibodies of the antikidney serum on the antigen in the kidneys of the animal receiving the injection. It is remarkable that a single injection of antikidney serum is frequently sufficient to produce a progressive type of chronic nephritis terminating in death from renal insufficiency.

Attempts to reproduce cardiac lesions by injecting antiheart serum have met with little success although Masugi claims to have obtained foci of fibrinoid necrosis in the heart of rabbits injected with the serum of ducks

immunized with rabbit heart. Aschoff bodies, however, were not described. Bauer reported pulmonary lesions resembling rheumatic changes in rats injected with anti-rat heart serum from rabbits. Pericardial lesions were produced in some rats when the serum was injected into the pericardial sac. No lesions were described in the heart muscle. It has been demonstrated by Burkey, Schwentker and Comploier, and Hecht et al. that staphylococcus toxin when injected with specialized tissues of the rabbit, as lens, muscle, kidney and skin, renders these tissue substances antigenic and initiates formation of antibodies to them.

It was proposed by Cavelti, in our laboratory, that if glomerulonephritis can be produced only by specific antibodies for kidney the same mechanism might be operating in rheumatic fever. In the latter case the myocardium and connective tissues generally would become antigenic and lead to the formation of auto-antibodies. Since the hemolytic streptococcus was under chief consideration as the etiological agent, it was assumed that this organism participated somehow in initiating this immunological response in the production of auto-antibodies and resulting in cardiac and other lesions in situ. The studies by Cavelti to test the mechanisms concerned have been carried on over a period of years and only a brief summary of his reports can be given here. The general plan of the experiments was to inject animals (rats, rabbits) with emulsions of certain tissues from the same animal species in mixture with killed Group A, beta-hemolytic streptococci and subsequently to attempt to demonstrate, in the serum of these animals, antibodies reacting in vitro with saline extracts of the respective tissue emulsions. For controls, animals were injected with either tissue emulsion or streptococci alone. Kidney, heart muscle, skeletal muscle and connective tissue were chosen for tissue emulsions.

Serological studies were made using the collodion particle technic wherein the collodion particles sensitized with the antigen were agglutinated upon addition of serum containing homologous antibodies. By the use of this method it was found that after repeated injections of the mixture of tissue emulsion and streptococci, about half of the animals developed antibodies reacting in vitro with saline extracts of the plain homologous tissue. Animals injected with streptococci or tissue emulsion alone failed to show the formation of such antibodies. There appeared to be little or no cross sensitization to different tissues except in the group of heart, skeletal muscle, and connective tissue. It is of interest that these auto-antibodies showed a peak about seven to 10 days after each injection schedule, and tended thereafter to disappear rapidly from the blood stream, possibly due to absorption by the homologous antigens in the tissues.

It would thus appear that tissue emulsions in association with the hemolytic streptococcus are capable of reacting in some manner with homologous tissues in the living animal to render the tissues antigenic. Whether this combination is with normal tissue elements or those injured by some fraction or product of the growth of the streptococcus is not clear. In the

pathogenesis of a disease such as rheumatic fever it would be assumed that some toxin produced locally in the throat, or some compound produced at the portal of entry, is carried throughout the body affecting blood vessels in many tissues, making them antigenic. Studies by Cavelti on glomerulonephritis by this technic are more convincing than in rheumatic fever. However, in animals treated with emulsions of cardiac and connective tissue and streptococci, cardiac lesions were produced in a substantial number of animals. The commonest lesions produced were valvular endocarditis with inflammatory infiltration and proliferation. In many instances the majority of the cells were of the large basophilic type, occasionally multinuclear and arranged in a more or less nodular fashion. Slight degenerative changes were sometimes observed in the intercellular connective tissues. Proliferative changes were noted in the valves in some animals. In the myocardium interstitial and perivascular changes were less often seen than in the valves, and at times there was widespread scarring but nodule formation was not often seen. Less often pericarditis and arteritis, and peri-arteritis of large and medium-sized vessels, were noted. Mixtures of emulsions of skeletal muscle, relatively free of connective tissue and streptococci, failed to produce cardiac lesions, suggesting that connective tissue may be of greater importance in producing auto-antibodies than muscle tissue.

A search for auto-antibodies in the serum of patients with active rheumatic fever by Cavelti gave promise of success in a group of patients studied, using as antigen the saline extract of one normal human heart. These results could not be repeated. Whether the antigenic substance is unusually labile or the auto-antibodies are only transiently found in the blood in patients with the disease, or for other unknown reasons, could not be determined.

These studies suggest that the etiological agent, presumably the hemolytic streptococcus, by injury to, or in combination with, the connective tissues of the body produces auto-antibodies which act in vivo to bring about lesions in the living animal which may be progressive or may be reactivated by repeated exposure to the same organism. Whether we can carry the analogy over into clinical medicine and apply it to glomerulonephritis and rheumatic fever and other diseases cannot be assumed unequivocally at this time, but it presents the most promising lead we have.

Summary

The pathogenesis of rheumatic fever is reviewed. The evidence that one or more strains of the beta-hemolytic streptococcus evoke a train of events leading to the clinical disease of rheumatic fever is convincing although not proved beyond question. The silent period following the initial symptoms in the pharynx suggests that some immune mechanism in the host is set in motion. Other immunological studies indicate that antibodies to the streptococcus are increased during this period. After the silent period the "trap is sprung" presumably by antigenic substances which are developed by the tissues of the host and perhaps are in the nature of auto-antibodies.

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USE OF ESTROGENS IN MEDICINE*

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ESTROGENS are substances which will provoke in numerous animal species the changes in tissues and in behavior which are known as estrus. Several steroids found in the adult female fit such a definition, the most potent being estradiol, from the metabolism of which are derived estrone and estriol. A variety of synthetic substances, not steroids, show similar estrogenic activities. The most widely known is diethylstilbestrol, and perhaps the most potent is dienestrol. Two great advantages of these synthetic compounds are their relatively lower cost and their slight loss of effectiveness when they are administered orally rather than parenterally. The disadvantage of synthetic materials is chiefly that a significant although small proportion of women receiving them report nausea or other unpleasant side-reactions, which are rarely noticed with the naturally occurring estrogens. Chemically altered natural estrogens have been prepared which share the advantage of high potency when taken orally. The commonest of these is ethinyl estradiol.

Natural estrogens may be secured from the graafian follicle liquor, from chorionic tissue, amniotic fluid, or most economically from the urine of pregnant mares. Crystalline pure single materials may be secured, although mixtures of several estrogens are known to be clinically effective. It is possible to use these natural estrogens either as free steroids, as the benzoate or propionate esters to delay absorption, or as the sodium salts of the estrogens conjugated with sulfuric or glycuronic acids, in which form they are found in urine.

The metabolism of estrogens is still known in only partial fashion. As described by Smith and Smith [1] estradiol is carried through a series of oxidative changes with formation of estrone and unidentified products which are no longer estrogenic. A small portion of the estrone is reduced to estriol. Only a small percentage of the estradiol can be recovered in urine in any of the estrogenically active forms. When progesterone is present, as during the third week of the menstrual cycle, or during pregnancy, the metabolic process is altered toward production of more estriol and less of the unidentified but estrogenically inactive products. These estrogenically inactive end-products are thought to stimulate the pituitary, which in turn stimulates the follicle to secrete more estradiol and also to ovulate and therefore to secrete progesterone. Under the influence of progesterone the alteration in metabolism of estradiol tends to reduced pituitary stimulation, thereby allowing decreased ovarian function and eventually menstruation. After progesterone secretion and activity have decreased, the original metabolic pathway

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for estradiol reappears, and the cycle is repeated. The Smiths report also that diethylstilbestrol acts in this regard like the estrogenically inactive products of estradiol, with potent stimulation of estrogen and progesterone production.

The biological effects of estrogens in women include the following:

1. Stimulation of myometrial growth
2. Stimulation of endometrial growth (tubular glands)
3. Stimulation of vaginal mucosal maturity
4. Stimulation of mammary duct growth
5. Stimulation of maturing changes in skin and its derivatives
6. Stimulation of secondary sex characteristics
7. Stimulation of union of epiphyses of long bones

In addition these steroids have some effects on salt and water balance, resembling the steroids of adrenal cortex origin. There are vasodilator effects of estrogens which may be important, even though not well understood. In addition to the effects upon the anterior pituitary already described it is known that large amounts of estrogens exert an inhibiting effect upon pituitary secretion, at least of the gonadotrophic hormones.

Diagnostic determination of estrogenic activity will include long term and short term effects. Over periods of months or years the best evidences of the action of estrogens are the presence of secondary sex characters, the proper timing of epiphyseal union, and the sustaining of regular menstrual rhythm or of fertility. These leave much to be desired in both quantitative features and in determination of the activity at a given time. For these latter needs the use of urine assays, chemical or biological, are not very helpful. Better information can be secured by use of the biopsy of endometrium [2] or the study of the exfoliated vaginal mucosal cells.[3] Recent evidence suggests that urethral cells may be at times an easily available substitute for vaginal cells.[4] The degree of progress from the small rounded cells of the deeper layers to the cornified and squamous cells of the outer layer of vaginal mucosa as seen in the material sloughing off spontaneously is the best of the semi-quantitative gauges of the intensity of estrogenic activity at any given time.

Therapeutic goals in use of estrogens may be the application of any one of the biological activities listed above. The most common is in the alleviation of the symptoms of the climacteric or menopause syndrome, in which field the experience with these preparations is greater than in all the others combined. The symptoms of the climacteric are most frequently due to a number of manifestations of autonomic nervous instability. In a few women this will resemble thyrotoxicosis sufficiently to constitute a problem in differential diagnosis. Exhibition of generous doses of any estrogen will produce symptomatic relief faster than can be achieved with iodine or with the antithyroid drugs. Frequently the climacteric syndrome has pronounced features of psychic distress, so that the diagnosis is an involutional syn-

drome. Endocrine therapy with estrogens is a most useful part of the program for the involution. Complaints about the joints are frequent, but the tissue changes involved are very poorly known. There may be some relationship to the early stages of osteo-arthritis. Estrogenic therapy in the early stages seems to afford not only subjective relief but also to restore normal outlines to the joint areas. Another type of osseous lesion seen late in the climacteric is osteoporosis.[5] This yields very slowly to use of estrogens.

Since several features of estrogen deficiency and the appropriate treatment belong essentially in the domain of gynecology, amenorrheas, menorrhagia, reduced fertility, vaginitis and kraurosis vulvae will not be discussed here. Dysmenorrhea is a problem faced by so many medical practitioners that it may be of interest to know that estrogens have been used with marked success in many cases of severe and recurrent pain. Hamblen and his associates [6] report that administration of generous doses daily from the fifth day of the flow for the next 20 days will eliminate the pain in most women. This is accompanied by suppression of ovulation and of secretion of progesterone. The benefits are purely temporary, as are any minor disturbances of the menstrual rhythm. Of course, fertility is reduced during such therapy. The cost of this treatment is not inconsiderable.

Occasionally there is failure to develop breast or uterine tissue during adolescence, and if the structures are not entirely lacking it may be possible to stimulate their growth by judicious and sustained therapy with estrogens. Exact procedures for this purpose are subject to clinical trial. It is suggested that estrogens should be administered in cycles, attempting to simulate the natural menstrual cycle of the ovaries, or if possible to supplement this cycle by careful timing of the doses.

Trials have been made with estrogenic therapy in control of acromegaly and of diabetes mellitus. These are based upon the inhibition of the anterior pituitary activity by large doses of estrogen. The success achieved is not striking. Synthetic estrogens may cause diabetes, at least in animals.[7] Use of estrogens to combat thyrotoxicosis has been reported, but is not dependable. Perhaps there is good reason to use these hormone materials in treatment of women with asthenic syndromes, provided there is evidence of deficient ovarian function in the patients. A quantitative diagnostic method is urgently needed before this type of therapy can be placed on an objective and sound basis. Empirical trials are safe if the physiological principles discussed above are kept in mind. Failures will be more frequent than successes, due in part to the many other causes of asthenia.

Estrogens may be administered via several routes: oral, parenteral, percutaneous, vaginal suppository, and subcutaneous pellet implantation methods being well known. The chief disadvantages of oral therapy are the requirement for larger doses than by the parenteral routes, and the risk of self-medication without professional advice. Oral therapy is nevertheless growing in favor as might be expected. Parenteral administration of

estrogens has usually been with solutions in vegetable oils, since the estrogens are so sparingly soluble in water that large doses could be administered only by repeated injection of large volumes. The oil solutions have been prepared with esters of estrogens which are slowly hydrolyzed and slowly absorbed, providing thereby a depot type of treatment, with benefits persisting from five to ten days after each dose. Since there are frequent unfavorable reactions to the introduction of such vegetable oils into muscle, the newer depot therapy is receiving favorable attention. This is based on either the pellet or the suspension of estrogen crystals in water. Pellets are absorbed slowly from their surfaces after having been placed in loose subcutaneous tissue spaces by small incisions or through trocars. Sometimes there have been local difficulties from foreign body reactions to these pellets. More recently the development of aqueous suspensions of very small crystals of certain estrogens has allowed the simple hypodermic injection of small volumes, following which the absorption of the crystals as they dissolve in tissue fluids provides sustained benefits for several days, comparable to use of oil solutions.

Vaginal suppositories were useful before the parenteral methods had been perfected, and continue to be helpful in treating vaginitis, where the local effect on vaginal mucosa is the important desideratum. This is now the case only in treatment of kraurosis or other atrophic conditions, under gynecological supervision.

Percutaneous administration of estrogens has had a curious history. When first proposed by manufacturers of cosmetic products it was resisted by medical men as being either futile or possibly a source of danger as a local carcinogen. It has been shown without any doubt that significant doses of estrogens can be absorbed through intact human skin, using either alcoholic solutions or ointments or creams. The fear of carcinogenesis has never been based upon authenticated cases, nor has all ground of fear been removed. Obviously the doses used would be of importance in this connection. The whole field of percutaneous administration of estrogens has had very little systematic study by qualified investigators. Systemic as well as local effects are involved. A recent review of the local activity of the sex hormones [8] presents little helpful information on this part of the problem, but points out the unfortunate exploitation of the public by purveyors of certain cosmetics. The remedy for such undesirable methods of treatment lies in careful study of the field by the medical profession.

Using any type of estrogen and any route of administration it is axiomatic that the doses must be made adequate by trial to achieve the therapeutic goal. Dosage needs almost always to be varied from time to time. This calls for professional judgment. Often large doses are required at first, and gradual reduction can be carried out without loss of control of the symptoms, as in the climacteric. Rather frequent and small doses are preferred to large doses at long intervals. The latter method tends to cause unduly rapid absorption of large amounts, with consequent temporary dis-

comfort, sometimes with exaggeration of menopausal tension states. If intervals between doses are too long, escape from control occurs, and the patient's lack of satisfaction is the result of the inadequate program.

Contraindications to use of estrogens come under several headings. Although it is probable that therapeutic doses of these hormones do not initiate the growth of carcinoma, it is possible that carcinomatous tissue of the genitalia or breasts may be made to grow faster in the presence of estrogens than without them. It is a matter of simple clinical caution to insist upon adequate physical examination before and at intervals during estrogenic therapy to make certain that no obvious malignancy is present. When there is malignant disease, or after carcinoma has been removed, it is considered unwise to use estrogens. Nevertheless there is recent evidence to suggest helpful treatment of certain types of breast cancer metastases in older women with these same substances.[9]

Endometriosis constitutes a contraindication to use of estrogens, since the symptoms are due to hyperplasia, secretion and bleeding from tissue which will atrophy only when estrogens are excluded, as by extirpation of ovaries. Other forms of treatment, such as with sedatives, cautious use of testosterone, or possibly with vitamin E, are available for women in the climacteric who have had endometriosis, as in carcinoma cases.

The other contraindications are quantitative, i.e. they are signals for reduced doses. Resumption of bleeding after the menopause suggests that the amount of estrogen employed is excessive. Menorrhagia in younger women has a similar significance. Of course, other causes of bleeding must be given consideration. Bothersome leukorrhea is more frequently a sign pointing in this same direction. Unwanted enlargement of the breasts and subjective tension states at times require reduction of dosage.

A word needs to be said for the woman whose symptoms require therapy with estrogens, but whose purse will not allow it. She still merits from her physician what he can and should do for her more fortunate sister who can purchase medication. With the rapidly expanded knowledge of the clinical significance of hormones, much of it has become available to our patients. Too often this is partial truth, and the consequence may be a mixture of unwarranted hopes and unnecessary fears. With his professional understanding of the problem the real physician will welcome the opportunity to present to each patient a simple explanation of her problem and of what he expects to do for her. There is no better way to achieve both gratitude and intelligent coöperation.

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A NOTE ON CORONARY OCCLUSION AND MYOCARDIAL INFARCTION FOUND POST MORTEM AT THE MASSACHUSETTS GENERAL HOSPITAL DURING THE TWENTY YEAR PERIOD FROM 1926 TO 1945 INCLUSIVE*

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Heart disease as a cause of death in this country today far exceeds all other causes. Coronary heart disease is one of the three most common types of cardiac involvement. Since this is so and since coronary occlusion and myocardial infarction are prone to involve in particular the leading citizens in every community, coronary heart disease has become a (perhaps *the*) most vital health problem that demands our attention. Its etiology is of prime importance and is now the subject of an extensive long range research at the Massachusetts General Hospital. In the course of preparing a background for our current and future studies, we have analyzed the post mortem records of this hospital over a period of 20 years. The results of this analysis we are briefly presenting herewith because of their interest and value as the experience of a large clinic concerned of late years with many cases of heart disease. The tables which summarize the data speak quite clearly for themselves and demand only brief comment and discussion. This report deals with the pathological findings per se. We have not included clinical or electrocardiographic correlations.

Incidence

A glance at table 1 demonstrates the fact that less than 25 years ago not only the practicing physician but even the pathologist himself was overlooking coronary heart disease, which certainly did not begin out of the blue 20 years ago and expand in its incidence in such a rapid degree. Even now it is easy occasionally to miss either coronary occlusion or myocardial infarction at autopsy. However, it is also probable that we do have under our care in the wards nowadays more cases with coronary heart disease than we had 20 years ago when they might have been treated at home or even overlooked altogether.

Site of Coronary Occlusion

It will be seen (table 2) that the anterior descending branch of the left coronary artery is by far the choice as a site for thrombus formation over all other sites in both acute and chronic cases, with the right coronary a poor

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TABLE I

Incidence of Autopsy Diagnosis of Coronary Thrombosis and Myocardial Infarction at the Massachusetts General Hospital 1926–1945 Inclusive

Year	No. of Autopsies	No. of Cor. Throm. and Myo. Infarct.	%	Year	No. of Autopsies	No. of Cor. Throm. and Myo. Infarct.	%
1926	170	0	0	1936	370	27	7.3
1927	167	4	2.4	1937	446	27	6.0
1928	220	9	4.1	1938	332	26	7.8
1929	225	7	3.1	1939	361	34	9.4
1930	299	9	3.0	1940	406	55	13.4
1931	371	23	6.2	1941	419	59	14.1
1932	374	17	4.8	1942	390	32	8.0
1933	394	27	6.9	1943	439	55	12.5
1934	420	29	6.9	1944	405	44	10.8
1935	436	21	4.8	1945	374	25	6.7

TABLE II

Distribution of Coronary Occlusions at the Massachusetts General Hospital 1926–1945 Inclusive

Arteries	Left Main	Anterior Descending	Left Circumflex	Ant. Desc. and Left Circumflex	Right	Right and Left	Total
Acute	16	127	36	3	78	19	279
Healed	18	161	45	36	29	54	343

second. In a moderate number of cases there were multiple sites, and quite a few of the fresh right coronary occlusions were found in cases with the left coronary already blocked, a condition which affords little chance for survival. The great majority of all these cases showed marked atherosclerosis of the coronary arterial tree, although there were some striking exceptions.

SITE OF MYOCARDIAL INFARCTION

The anterior wall of the left ventricle supplied by the descending branch of the left coronary artery was much the most common location of infarction (table 3), being almost twice as common as the posterior site, while lesions limited to the septum or right ventricle were quite infrequent. However, in 72 of the 190 hearts with fresh anterior myocardial infarction there was an

TABLE III

Site of Myocardial Infarctions at the Massachusetts General Hospital 1926–1945 Inclusive

Infarction	Total	Anterior	Posterior	Septal	Rt. Vent.	Ant. and Posterior	Recent and Healed
Recent	267	190	109	5	8	45	74
Healed	289	222	122	5	2	62	

extension into the adjacent portion of the septum, which was also true in 35 of the 109 hearts with fresh posterior infarcts. The size of the infarcts varied from 0.3 cm. by 0.1 cm. to 12 cm. by 15 cm. In many cases the lesion involved the entire thickness of the wall but sometimes extended only half or three quarters of the distance.

Association of Coronary Occlusion and Myocardial Infarction

Table 4 clearly shows that coronary occlusion and myocardial infarction are not synonymous, as was once thought, and as is still often unfortunately implied in diagnostic terminology. In fact only half of the cases of recent coronary occlusion showed infarcts. The classical work of Schlesinger and

Table IV

Association of Coronary Thrombosis and Myocardial Infarction at the Massachusetts General Hospital 1926–1945 Inclusive

Myocardial Infarction			Coronary Thrombosis		
Total Recent	Associated with Cor. Occl.	Unassociated with Cor. Occl.	Total Recent	Resulted in Myo. Infarct.	Not Resulted in Myo. Infarct.
267	162 (60.6%)	105 (39.4%)	261	131 (50%)	130 (50%)

Blumgart clarified this discrepancy for us years ago. Also as these authorities noted there may be a lack of correlation between the site of the acute occlusion and the site of the infarct due to previous occlusions and the development of a collateral circulation. Thus in our series there were 12 cases with fresh anterior myocardial infarcts and acute occlusion of the right coronary artery in 11 and of the left circumflex in the remaining one with old occlusion of the left anterior descending artery.

Cardiac Aneurysms and Ruptures

Large cardiac aneurysms due to myocardial infarction we found in 10 per cent of cases (table 5) although aneurysmal concavities of small degree with shallow depression are commonly present. Both large and small aneurysms are likely to be the site of mural thrombi. Rupture of the ven-

Table V

Cardiac Aneurysms and Ruptures at the Massachusetts General Hospital 1926–1945 Inclusive

Kind	Total No.	Anterior		Posterior	Septal
			Lt. Rt.		
Aneurysm	52	38		11	3
Rupture	23	21	1	0	1

tricular wall at the site of an acute myocardial infarct occurred in less than 5 per cent of all these coronary cases. Both aneurysms and ruptures were preponderantly in the anterior wall of the left ventricle. In one case involving the septum, a ventricular septal defect resulted.

Mural Thrombosis with Myocardial Infarction

We do not always appreciate how commonly thrombosis occurs within the ventricular cavity, mostly the left, and elsewhere as well as over the site of acute infarcts (table 6). Since such thrombi are often the cause of peripheral arterial embolism a strong argument exists for the use of anticoagulants early in the course of the acute illness.

Table VI

Association of Mural Thrombi and Myocardial Infarction at the Massachusetts General Hospital 1926–1945 Inclusive

Myo. Infarct. Recent and Healed	No. of Cases with Mural Thrombi	Mur. Throm. with Myo. Infarct.	Fresh Throm. with Acute Myo. Infarct.	Organized Throm. with Healed Myo. Infarct.	Unassociated with Myo. Infarct.
489	232	175 (32.7%)	112 (41.0%)	58 (26.1%)	43

Systemic Arterial Embolism

Of the 207 cases with thrombi in the left heart chambers (table 7), 95, almost half, had complicating embolism of the cerebral, renal, splenic, or limb

Table VII

Association of Mural Thrombi and Arterial Embolism at the Massachusetts General Hospital 1926–1945 Inclusive

Total Thrombi in Lt. Heart	No. of Cases with Art. Emb.	Art. Embol. with Thrombi in Left Heart	Art. Embol. without Thrombi in Left Heart
207	153	95	58

arteries or even of the aorta itself. There were half as many cases again with peripheral arterial block who showed no such thrombi in the left heart itself; evidently the embolus constituted the entire thrombus.

Pulmonary Arterial Embolism

We have come to know well the frequency and seriousness of pulmonary embolism (table 8) as a complication of acute myocardial infarction and to realize that such embolism has its origin rarely from intracardiac thrombosis but almost invariably from an often unrecognized leg vein thrombosis. This helps to explain the discrepancy between the 106 cases of pulmonary embolism in the present series and the 36 cases of that condition which showed

TABLE VIII

Association of Pulmonary Infarction and Myocardial Infarction
at the Massachusetts General Hospital
1926–1945 Inclusive

Total Pul. Infarct.	With Rec. Myo. Infarct.	With Healed Myo. Infarct.	With Recent Ant. Myo. Inf.	With Recent Post. Myo. Inf.	No. Throm. in Rt. Heart
106	60 (20.9%)	46 (20.7%)	29 (15.3%)	31 (28.4%)	49 (36 with pul. inf. 13 without pul. inf.)

thrombi in the right heart chambers. Even in this latter group the leg veins rather than the heart were probably the site of the offending thrombi. Until recent years, however, the leg veins have not been investigated in such cases post mortem.

PERICARDITIS COMPLICATING MYOCARDIAL INFARCTION

The pericarditis (table 9) found with either acute or healed myocardial infarction was never serious per se and usually only slight to moderate in degree. It occurred in about a third of the acute and a quarter of the chronic cases. Quite possibly it had left little or no trace in some of the healed cases.

TABLE IX

Association of Myocardial Infarction and Pericarditis
at the Massachusetts General Hospital
1926–1945 Inclusive

Recent Myo. Infarct.	Acute Pericarditis	Healed Myo. Infarct.	Pericardial Adhesions
267	92 (34%)	222	61 (27.5%)

PROGNOSIS

This postmortem analysis affords little information as to prognosis in coronary occlusion or myocardial infarction. There were, however, more cases in this 20 year period with healed or chronic lesions of both categories than with acute (tables 2 and 3); not infrequently, though in a minority of cases, acute coronary occlusion or myocardial infarction was superimposed on the hearts with chronic or healed scars but more often there was but the one process, fresh or old. Some other disease was responsible for death in not a few of the chronic cases. So far as the relative prognosis according to site of the lesion was concerned there was little to choose, though anterior myocardial infarcts seemed to be slightly more likely to lead to rapid death. In the total series there were 84 cases that died within a few seconds to a few hours of the acute heart attack which not infrequently occurred itself unexpectedly on the ward in the hospital. Of these 84 cases, 35 showed fresh anterior myocardial infarcts, 15 fresh posterior infarcts, and 34 acute coronary occlusion without infarction, 18 of which involved the left coronary

artery and 16 the right. Of another 108 cases who died of their acute heart disease within a few days but survived the first few hours, 51 showed anterior infarcts, 26 posterior, 20 both anterior and posterior, six right ventricular alone, and five septal alone. It is to be remembered that anterior myocardial infarcts exceeded in number posterior infarcts in the total series, both in the acute and in the chronic stages, 190 to 109 in the case of the acute and 222 to 122 among those healed. Despite that fact, however, the somewhat greater seriousness of the anterior infarcts was borne out particularly by the incidence of cardiac rupture which occurred in 22 cases of anterior infarcts, 1 case of septal infarct, and in no case of posterior infarct.

Conclusion

An analysis of the post mortem records at the Massachusetts General Hospital over a period of 20 years (7,018 cases) has revealed an increasing incidence of the diagnosis of coronary occlusion and myocardial infarction from a very low figure in 1926 to percentages of 13 to 14 in 1940 and 1941; a change to be attributed in part at least to a more active search for these lesions. Occlusion of the left coronary artery, involving preponderantly the anterior descending branch, was much more common, especially in the chronic stage, than occlusion of the right coronary. Anterior myocardial infarcts, both recent and healed, were nearly twice as common as posterior myocardial infarcts; not infrequently one was superimposed on the other, i.e. a fresh lesion in a heart with an old scar. The anterior myocardial infarcts were somewhat more serious than the posterior; this was particularly shown in the case of ruptures of the heart which occurred through the *anterior* wall in 22 of the 23 cases. Coronary occlusion and myocardial infarction did not always coincide and should not be considered as synonymous.

EFFECT OF INTRAVENOUSLY ADMINISTERED OXYGEN ON SYMPTOMS AND VITAL CAPACITY IN BRONCHIAL ASTHMA *

By Harry Markow, M.D., Mendel Jacobi, M.D., F.A.C.P., Henry Rascoff, M.D., F.A.C.P., Benjamin Kogut, M.D., and Romeo W. Auerbach, M.D., *Brooklyn, New York*

Gaseous oxygen has long been administered intravenously to animals without deleterious effects.[1] Attempts have been made sporadically over many years to utilize the intravenous route for the administration of oxygen in cases of anoxia in man.[2] These attempts were not continued further because of the development of such undesirable effects as embolism or cardiac tamponade. An analysis of these attempts shows that the amounts of oxygen administered were too large or that the gas was injected too rapidly or at too high a pressure. Ziegler,[3] in 1941, described an apparatus for administering pure (commercial 100 per cent) oxygen intravenously at low pressures and in physiologic amounts, and mentioned its use by this route for several patients with various forms of anoxemia. He noted no deleterious effects, but gave no details of diagnosis or results.

During the previous investigation by some of us of the effects of intravenously administered 100 per cent (commercial) oxygen in experimental shock in animals, and in three cases of severe acute progressive (secondary traumatic) shock in human beings,[4] occasion arose to study the effects of oxygen so administered, on the vital capacities of a group of patients suffering from severe, long-standing bronchial asthma of the perennial type. All the patients in this study gave histories of long-standing, frequently recurring asthmatic attacks; all were experiencing a diminishing response to bronchodilators during the attacks; all showed markedly diminished vital capacities when tested during attack-free intervals, a finding at variance with that of Feinberg.[5] As pointed out by Westcott and Gillson,[6] vital capacities are diminished in long-standing bronchial asthmatics, even during intervals between attacks.

As a corollary to the above studies, we attempted to correlate the frequency and severity of the asthmatic attacks with the vital capacity levels, such levels being determined at periodic intervals following the intravenous oxygen therapy. It had previously been shown by Westcott and Gillson [6] that the increase in vital capacity obtained in that study by means of exercises, postural drainage and epinephrine inhalation therapy was associated

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with symptomatic improvement for periods up to nine months; and that the greatest degree of improvement occurred in those cases initially showing the greatest diminution in vital capacity. From a reading of their paper, it appears that the prescribed exercises and inhalation therapy were continued throughout the period of study. In our cases, intravenous oxygen was administered in single or divided doses during one period of hospitalization and was not thereafter repeated while under subsequent clinical observation.

All our patients showed evidences of stagnant and anoxic anoxia. The latter is found in true bronchial asthma, and is due to the incomplete saturation of the blood leaving the lungs which may be observed in any form of respiratory depression. The former is also encountered in bronchial asthma, and is often an important factor when poor cardiac function, with decreased blood volume and delayed pulmonary circulation time, is superadded.[7] Anoxic anoxia was of importance in cases 5, 6 and 7 of this series. No cases of anemic anoxia were encountered.

It has been shown in cases of shock that a change from a 95 per cent oxygen—5 per cent carbon dioxide inhalant mixture to a 100 per cent oxygen inhalant causes a marked rise in oxygen partial pressure (from 14 to 21 mm.), with a 50 per cent rise in oxygen availability to the body tissues.[8] In asthmatic attacks the alveolar ventilation is usually poor to a considerable degree, due to the muscle spasm of the bronchioles and to the frequently present intrabronchial and intra-alveolar exudation. That pulmonary exudates may actually be interstitial, and not demonstrable as clinical edema with râles, was pointed out by Drinker[9]; they may, however, effectively impede the transport of oxygen to the pulmonary alveolar capillaries. This can be realized at a glance, when it is noted that the diffusion coefficient of oxygen through the pulmonary epithelium of the intact animal (i.e., the number of cubic centimeters absorbed per minute per millimeter of mean pressure difference between the the blood and alveolar air) varies between 23 and 45, while the diffusion coefficient for oxygen through water (at body temperature) is 0.51.[10] It is for this reason that it was deemed advisable to attempt to by-pass a functionally deficient lung by means of the intravenous administration of oxygen.

As pointed out in our previous communication,[4] there is no danger of air-embolism or vapor lock if the intravenous administration of oxygen is carefully regulated and kept within physiologic volume, pressure and flow-rate. It may again further be emphasized that pure oxygen is utterly dissimilar from air; the former is entirely respirable; the latter, i.e. air, is low in oxygen content (20.94 volume per cent) and is composed almost wholly of irrespirable gases (79.02 volume per cent of nitrogen and other inert gases). Finally, though air-embolism is the perpetual bête-noir of medicine, it is, in actual experience, as pointed out in our previous paper, a rarity.

Method of Study

Eight of nine patients with severe long-standing perennial asthma were selected from the clinic, where they had been observed for a number of years; one was admitted to the clinic after participating in this study. The records of these patients indicated that their asthmatic attacks had been increasing in frequency and severity and that the usual forms of therapy had become ineffectual. At the time this study was begun, each patient had been having repeated asthmatic attacks daily for a prolonged period of time. Some were skin sensitive, others skin negative on test. Upon admission to the hospital, vital capacity determinations,* in duplicate, were made when the patient was in a free interval. In cases 5, 6 and 7, electrocardiograms were taken prior to the administration of oxygen. Blood counts, taken on all patients, showed no abnormal findings. In particular, there was no anemia.

When two successive vital capacity determinations showed figures in agreement to 2 per cent, the oxygen administration was begun. Using the Ziegler technic and apparatus,[3] 100 per cent (commercial) oxygen was administered intravenously at a rate of 600 c.c. per hour, and at a pressure just sufficient to clear the glass viewing tube, proximal to the intravenous needle, of the blood that had refluxed into it upon venipuncture, i.e., a pressure just above venous pressure. The intravenous oxygen was allowed to flow for periods of from two to 17 hours without interruption, except when it became necessary to clear the needle of the occasional clot that formed. In two cases (1 and 8) a single course of intravenous oxygen was administered. In three cases two courses were administered (case 3: 17 and four hours; case 4: 15 and 10 hours; case 7: 12 and 12 hours). In three cases three courses were administered (case 2: 15, six and two hours; case 6: 14, 14 and 10 hours; case 5, five, two and four hours). Vital capacities were again determined, with the patient not in an attack, on the day after the oxygen was discontinued or upon discharge from the hospital. In the cases in which the oxygen was administered in divided doses, vital capacity determinations were performed just before each administration. In cases in which asthmatic attacks occurred during the period of study in the hospital, at least four hours, in which the patient was symptom-free, were allowed to elapse before vital capacity determinations were performed.

After the oxygen was finally discontinued, the patients were discharged, to be followed up in the clinic. A daily record of the number and severity of attacks was kept. Vital capacity determinations, all again during an attack-free state, were made at intervals during the succeeding year. After discharge from the hospital, some of these patients did not return to the clinic for periods of from two to four weeks, and in this period they received no other form of therapy.

* The McKesson water spirometer was used in these determinations.

Case Reports

Case 1. D. G., age 45, housewife, was admitted to the allergy clinic September 1940 with a history of perennial attacks of bronchial asthma of 20 years' duration associated with fall hay fever and a fall aggravation of the asthmatic attacks. Since 1939 the attacks had become more frequent and severe.

Examination revealed an obese, white female, weighing 224 pounds, with a typical asthmatic chest, infected tonsils, and a blood pressure of 156 mm. Hg systolic and 90 mm. diastolic. Roentgenogram of the lungs was negative; roentgenogram of the sinuses showed a membranous thickening of ethmoids and maxillary antra. Nasal examination did not reveal clinical evidence of sinusitis. The blood smear showed 8 per cent eosinophiles. On test, she showed positive reactions to ragweed, dust and kapok and a marked reaction to silk which test was followed by a constitutional reaction controlled with adrenalin.

Specific therapy was begun in January 1941 with ragweed and dust extracts and an autogenous vaccine, and was continued regularly up to her admission to the hospital with moderate improvement but without freedom from symptoms at any time. Exacerbations occurred during the summer and fall months. Prior to admission to the hospital on October 5, 1942 she had had daily recurring attacks of asthma during August and September so persistent that, as she stated, "I was afraid to go to bed." These attacks were still present at the time of her admission to the hospital. The vital capacity determination on October 6, 1942 was 1,600 c.c.

Intravenous oxygen was begun at 11:00 a.m. on October, 6, while asymptomatic, and was given continuously for 14 hours. Prior to this, the patient always complained of coldness of the extremities. Immediately after the beginning of intravenous oxygen she felt a flushing and warmth of the left side of her body (left arm injected) and two hours later the right side felt warm, while the left side of her body cooled off. During this therapy she developed a mild wheezing spell that lasted five minutes. In all, she received 8,000 c.c. of intravenous oxygen in 14 hours. She was discharged from the hospital October 7, 1942. The vital capacity determination on October 7 was 2,100 c.c., an increase of 500 c.c., or 31 per cent over pretreatment level.

On October 15, 1942 she returned to the clinic and reported that she had been free of asthma except for one five minute attack after going through the contents of an old trunk. She felt definitely improved, was free of nocturnal attacks although coughing, and now was able to walk without symptoms, although previously the mere walking from one room to another resulted in difficult breathing and wheezing. She stated that she breathed more deeply and more freely now and that the act of talking was no longer associated with a choking sensation and tightness in her throat. Subsequent vital capacity studies showed the following:

October 28, 1942:	2,100 c.c.
November 4, 1942:	2,100 c.c.
February 3, 1943:	1,700 c.c.
March 29, 1943:	1,500 c.c.

During this six month period she continued to attend the clinic regularly, receiving specific therapy. In that time she had one attack of asthma and an occasional mild wheezing spell. Although this apparent improvement coincided with the termination of the fall hay fever season, such improvement had not occurred in previous years at a similar time. Since this therapy there has been a decided improvement in her case up to the present time. The coseasonal asthmatic symptoms have now been reduced to a mild wheeze, and the perennial nasal symptoms have practically disappeared. In all, she received 8,000 c.c. of oxygen in one period of 14 hours with a

maximal increase in vital capacity of 500 c.c., or 31 per cent, which was maintained for a period of one month and this slowly diminished to pretreatment level after five months.

Case 2. B. R., age 18, hospital employee, was admitted to the allergy clinic June 7, 1941 with a history of hay fever from August to October of 1938 and with a recurrence of symptoms during December of 1938. In 1939 she had had similar symptoms from August to October with a similar recurrence in December of the same year. In 1940 hay fever symptoms appeared from April to June and from August to October. Asthmatic attacks occurred during these periods, requiring adrenalin injections by an ambulance physician on several occasions. Prior to admission to the clinic in June 1941 she had had frequent severe asthmatic attacks complicating her hay fever. There was a history of frequent upper respiratory infections. She had had infantile eczema. The familial history included hay fever in her mother, asthma in her paternal grandfather, hay fever in two maternal uncles, one aunt and one first cousin, and one paternal first cousin. Her blood count was normal.

On test, she was sensitive to the pollen of ragweed, grasses and trees, to dust, cat and dog epithelium, horse serum and feathers. There were slight and moderate reactions to a variety of foods which were thereupon eliminated from the diet. Roentgenogram of the sinuses revealed clouding of the ethmoids and sphenoids and veiling towards the floor of both maxillary antra. Roentgenogram of the lungs was negative. Frequent nasal examinations revealed the presence of a purulent paranasal pansinusitis.

During the first year treatment at the clinic with specific therapy and local nasal therapy resulted in no improvement in either the hay fever or asthmatic symptoms. She was admitted to the hospital on October 12, 1942 after having had daily recurring attacks of bronchial asthma for two months. Her description of the symptoms revealed that she went to bed feeling well and invariably an asthmatic spasm occurred within two to three hours. The vital capacity determination on admission was 2,100 c.c.

After three hours in bed, a severe attack developed. Intravenous oxygen was begun at 5:40 p.m. Within five minutes she reported that the difficult breathing had ceased, although on auscultation wheezing respirations were still audible. Before the oxygen was started, her entire body felt cold but within five minutes this passed into a feeling of general body warmth. After one hour of oxygen therapy, labored breathing again appeared and the needle was found to be clogged. After the intravenous oxygen flow was reinstituted, the dyspnea immediately again disappeared. After two hours, although the wheezing respiration was still present on auscultation, she was comfortable and there were no subjective signs of asthma. At one point, when the pressure of the flow of oxygen accidentally became too great, she felt choked and dizzy but this passed when the pressure of the flowing oxygen was reduced. At 9:00 p.m. she was resting comfortably, although occasionally wheezing and coughing, but she did not appear to be in an asthmatic attack. After eight hours, the oxygen was discontinued. On the following day, October 13, she felt exceptionally well, remarking after the vital capacity was taken that, "I can now take a deeper breath than I can remember." The vital capacity determination on October 13, 1942 was 2,500 c.c. as compared with the initial reading of 2,100 c.c.

At 7:00 p.m. that day she developed another severe attack of asthma while talking to a visitor. At 7:30 p.m. oxygen was started intravenously and within five minutes there was relief of the dyspnea although wheezing could be heard. She experienced a feeling of warmth over the entire body which persisted as long as the oxygen flowed. At 9:10 p.m. the oxygen was discontinued when the patient appeared to be comfortable. She slept well until 6:00 a.m. on October 14, when another severe attack occurred. Intravenous oxygen was started at 6:30 a.m. producing bodily warmth within five minutes and relief of dyspnea within 30 minutes. Oxygen was discon-

tinued at 10:000 a.m. The vital capacity determination on October 14, 1942 was 2,400 c.c.

During the remainder of that day and the following night the patient was comfortable. On October 15, 1942 a mild attack of asthma was relieved by five minims of adrenalin. The vital capacity determination on the day of her discharge from the hospital, October 15, 1942, was 2,800 c.c. In the following two weeks she was asthma-free for the first time in three months although still coughing. Subsequent vital capacity studies showed the following:

October 17, 1942:	2,800 c.c.
October 28, 1942:	2,800 c.c.
November 4, 1942:	2,800 c.c.
February 3, 1943:	2,200 c.c.
June 1, 1943:	1,300 c.c.

On October 28 and 29, 13 and 14 days after her discharge from the hospital, she had two mild wheezing spells in the early morning hours lasting about 20 minutes. On December 2, 1942 she had an attack of asthma while walking in a heavy wind. Since then, and up to June 1, 1943, she attended the clinic regularly, continued to receive specific therapy and had an occasional cold and sore throat but no asthmatic attacks except on May 28, 1943 following the ingestion of fish. During the hay fever seasons of 1943 and 1944 she was asthma-free although she coughed and had an occasional wheeze.

In all she received 11,500 c.c. of oxygen during a two day interval which was divided into periods of 15, six and two hours each. There was an increase in vital capacity of 700 c.c., or 33 per cent, which slowly diminished to pretreatment level within four months and then further diminished beyond that in nine months.

Case 3. K. B., housewife, was admitted to the allergy clinic on July 29, 1937 at the age of 29 complaining of perennial attacks of shortness of breath, wheezing and choking since the age of 27. At first these attacks were infrequent, generally preceded by colds and worse in winter months. In the two months preceding her admission to the clinic, the attacks occurred daily. The personal and family history was negative. There were no hay-fever symptoms.

Examination revealed poor teeth, inflamed gums and a red and inflamed throat. The heart was negative. There were many sibilant and sonorous râles in both lungs. The blood pressure was 125 mm. Hg systolic and 80 mm. diastolic. On test she reacted moderately to dust, feathers, kapok and orris root. There were only slight reactions on test and retest to plantain and ragweed. The roentgenogram of the chest was negative; roentgenogram of the teeth showed retained root fragments, an apical abscess of the left lower bicuspid and a rarefaction about the roots of the left upper cuspid. The nasal examination revealed polypoid degeneration of both midturbinates. On roentgenogram, both ethmoids were cloudy, especially the right. The Wassermann reaction was negative. A blood count showed hemoglobin 14.8 gm., red blood cells 4,100,000, white blood cells 6,000 with 2 per cent eosinophiles.

She was treated with food and inhalant elimination and substitutions and hyposensitized with extracts of dust and feathers. She also received stock vaccine as well as local nasal treatment. After five infected teeth were extracted she improved until the fall of 1938. As a result of an aggravation of clinical symptoms during the ragweed season, ragweed injections were added to the treatment in spite of only slightly positive skin sensitivity. The following year, with exacerbation during the grass season, retests remained negative to timothy but moderate with itching to plantain, and plantain injections were added to her treatments. In spite of high ragweed dosage during 1939, there was little improvement in her symptoms during that year.

These symptoms continued through the winter of 1939 and the early part of 1940. On retest, positive reactions to timothy appeared for the first time and this was then added to her treatment. During this period, she was under observation and treatment by the otolaryngologist but little evidence of infection was found although polypoid degeneration of the mid-turbinates persisted. She continued moderately asthmatic with a persistent cough through 1941 and, in spite of pollen therapy, there was no relief during the pollen seasons. Some attacks could be traced to specific food sensitivity, especially fish and nuts. Toward the end of 1941 she began to show moderate reactions to various trees and in the spring of 1942 showed a marked reaction on test to timothy in weak concentrations. She was somewhat improved in the first half of 1942 but thereafter her asthma gradually became more severe and persistent. Examination failed to reveal active infection in the sinuses. She was admitted to the hospital October 16, 1942 having had daily recurring severe attacks of bronchial asthma since August. The vital capacity determination on admission was 800 c.c.

On October 17 and 18 she was comfortable with barbiturates and rest in bed, although she wheezed and had slight difficulty in breathing for which she did not require adrenalin. On October 19 at 6:45 a.m. she received a small dose of adrenalin for the relief of a mild asthmatic attack. At 5:00 p.m. on the same day, the asthma became more pronounced and intravenous oxygen was started. In 15 minutes she was relieved, after feeling warm all over her body and perspiring freely. Oxygen was continued throughout the night and was discontinued at 9:00 a.m. on October 20, 1942, after 17 hours, at which time she stated that her lungs felt clear and that she could breathe easily and freely. During that night she slept intermittently. The vital capacity determination on October 20, 1942 was 1,200 c.c., an increase of 400 c.c. On October 20 at 8:00 p.m. oxygen was again started and discontinued at 12:30 a.m. on October 21, after four hours. During this period she slept and was fairly comfortable. The vital capacity determination on October 21, 1942 was 1,500 c.c., an increase of 700 c.c. over the initial reading. She continued comfortable during the day and night of October 21 and was discharged from the hospital on October 22 at noon. She remained symptom-free for four days until October 26, 1942 when mild wheezing began and this continued until October 31, 1942. This was attributed to the ingestion of fish on two occasions during that week, contrary to instructions. Subsequent vital capacity studies showed the following:

November 4, 1942: 1,400 c.c.
February 3, 1943: 1,200 c.c.
May 23, 1943: 1,000 c.c.

On January 7, 1943 she reported that she had contracted a cold, precipitating a severe asthmatic attack which responded promptly to sulfa therapy. A discharging ear which complicated this infection did not respond to sulfa therapy. On April 1, 1943 she reported a mild asthmatic spell following another upper respiratory infection.

In all she received 9,000 c.c. of oxygen in two periods of 17 and four hours respectively, with an increase in vital capacity of 700 c.c., or 87 per cent. This increase was maintained for two weeks and fell to a level of 25 per cent above the pretreatment vital capacity at the end of six months.

Case 4. B. M., age 45, printer for 20 years, was admitted to the clinic on August 1, 1940 with a history of severe and persistent attacks of bronchial asthma since January 1940. During his initial attack, he was admitted to a county hospital where nasal surgery was performed for an infection of the sinuses and a deviation of the septum. Following this, he improved until May 1940 when nightly attacks recurred, relieved by adrenalin injections. During July, the month prior to his admission to the clinic, he had two or more attacks of asthma nightly. The family history was negative for allergy.

Examination revealed hypertrophied and diseased tonsils. Nasal examination revealed a bilateral purulent discharge in both ethmoid and sphenoid areas. Transillumination of the sinuses showed an absence of aeration of both antra and of the left frontal sinus. Antral washes yielded large flakes of pus from the right side; the left was negative. Roentgenographic examination showed a veiling of the left frontal sinus and both ethmoid and maxillary sinuses. A diagnosis of paranasal sinus infection was made. The heart was negative. Many sonorous râles were heard throughout both lungs. Skin tests were essentially negative except for a moderate reaction to dust and feathers. The blood count showed hemoglobin 12 gm., red blood cells 3,990,000, white blood cells 5,000 with 4 per cent eosinophiles. Urinalysis was negative.

During the following year he received local nasal treatments, refusing further surgical intervention because of the apparent failure of previous surgery to give lasting relief. Hyposensitization with dust extract and injections of a stock catarrhal vaccine did not afford any relief from his attacks. His attacks became more severe and more frequent. He obtained moderate relief for about two hours with adrenalin injections during these attacks. From May 1941 to September 1941, he received a course of caffeine sodium benzoate injections, at first daily and then twice weekly with fairly good results, but this was discontinued because of his extreme nervousness and apprehension. Following the cessation of this therapy, he had three to four attacks of asthma daily. During the month of October 1941 he was bedridden and required adrenalin injections daily by the ambulance surgeon for relief. Following surgery for acute appendicitis in 1941, his attacks became milder and less frequent. In December 1941 and in January 1942, he spent eight weeks in bed with further severe asthmatic attacks of varying intensity and duration, requiring one to two adrenalin injections daily. The regimen, consisting of iodides by mouth, adrenalin by inhalation, local nasal therapy and injections of dust and vaccine, yielded very little relief. Dietary control was carefully observed. From March to October 1942 there was no apparent improvement in either the severity or the frequency of his asthmatic attacks. Pollen retests remained negative. Oral nicotinic acid at first eased the attacks, but this effect was soon lost. Repeated nasal examinations still revealed the presence of bilateral ethmoiditis. He was admitted to the hospital on October 27 at 1:00 p.m. in a mild asthmatic attack. The vital capacity determination on admission, before instituting treatment, was 2,200 c.c.

On October 28 a severe attack of asthma was reported at 7:00 p.m. Intravenous oxygen was started immediately and was continued until 10:00 a.m. on October 29. In one-half hour he felt a warmth over his entire body, especially the back of his chest, and the attack of asthma was relieved in two hours. He slept through the night while under the intravenous therapy. During the next 12 hours he reported that he felt very well. The vital capacity determination on October 29, 1942, during an asymptomatic period, was 2,700 c.c., an increase of 500 c.c. or 23 per cent over the pretreatment level.

On October 29, at 10:00 p.m., he again developed an asthmatic attack. Intravenous oxygen was started at 10:30 p.m., and was continued until 10:00 a.m. the following morning, October 30. Within 15 minutes after the oxygen therapy was begun, he developed a warmth of the body and a total cessation of the asthmatic symptoms. He slept throughout the night while receiving oxygen therapy. The vital capacity determination on October 30, 1942 was 3,200 c.c., a further increase of 500 c.c. with a total increase of 46 per cent over the pretreatment level. He felt very well that day, was free from symptoms the following night, and was discharged from the hospital the morning of October 31, 1942.

Following his discharge, he had two mild asthmatic spells on two days during the first week and none in the following two weeks. He felt well enough during this

period to try out the effects of physical exercise on his symptoms, since he previously could not walk more than five blocks without developing dyspnea and wheezing. Now he was able to walk 25 blocks before he noticed shortness of breath or wheezing. This mild attack lasted but 30 minutes and subsided. He was asthma-free for the first time without ephedrine or adrenalin medication although he still coughed and had spells of wheezing. The feeling of oppression of his chest was gone and he felt that he was breathing more easily and deeply. Subsequent vital capacity studies showed the following:

November 4, 1942: 3,200 c.c.
November 11, 1942: 3,200 c.c.

During the following six months he complained only of occasional mild wheezing which was readily relieved by medication. In all he received a total of 18,000 c.c. of oxygen in two periods, 15 and 10 hours, with an increase in vital capacity of 1,000 c.c., or 45 per cent over the pretreatment level, with a marked clinical improvement. After the oxygen therapy he had but one severe attack of asthma in six months, in addition to several mild attacks and an occasional spell of wheezing.

Case 5. K. K., age 55, a presser by occupation, was admitted to the allergy clinic on August 13, 1942 with a 25 year history of recurring perennial attacks of choking, wheezing, coughing and labored breathing, usually associated with, or following, upper respiratory infections. In the few years prior to his admission, the symptoms were continuous and severe, with no seasonal or occupational exacerbation. An uncle had asthma.

Examination revealed a small, poorly nourished and developed individual, markedly dyspneic, with a marked retraction of the clavicular fossae and intercostal spaces. Auscultation revealed many sibilant and sonorous râles in both lungs. The heart sounds were distant; there were no murmurs. The blood pressure was 110 mm. Hg systolic and 70 mm. diastolic. An electrocardiogram was suggestive of moderate myocardial damage.

Allergy tests were negative, except for a moderate reaction to dust extract. The nasal examination revealed an allergic type of mucous membrane. On transillumination, all sinuses illuminated clearly except the left maxillary antrum which was practically opaque. Roentgenographic examination showed a clouding of the left maxillary antrum and the presence of an osteolytic destruction of the lateral wall of the left maxillary antrum suggestive of a neoplasm. Roentgenographic examination of the lungs revealed fibrobronchiectasis and old tuberculosis. In addition, there was reported a dense shadow along the outer aspects of the right thorax, opposite the eighth and ninth ribs, encroaching upon the soft tissues, probably of a neoplastic nature. Similar findings, unchanged, were reported upon roentgenographic examination on May 5, 1944, almost two years later. The blood count showed hemoglobin 93 per cent, red blood cells 4,530,000, white blood cells 6,800, with 64 per cent neutrophiles and no eosinophiles. Urinalysis was negative. Sedimentation rate was 18 mm. in 100 minutes. Blood Wassermann reaction was negative.

The patient was initially admitted to the hospital in August 1942 for study of the tumor of the left antrum, but he refused a biopsy and was discharged in a few days. Severe asthmatic dyspnea continued, however, and he was readmitted to the hospital on October 31, 1942 for intravenous oxygen therapy. The vital capacity determination on the day of admission, during a symptom-free period, was 700 c.c.

Shortly thereafter, he developed an asthmatic attack. Intravenous oxygen was started at 2:00 p.m., the day of admission. At 2:05 p.m. he stated that he was breathing more easily. Objectively, he appeared more comfortable and his respirations were less labored. Intravenous oxygen was continued for five hours. In the third hour of the therapy he developed a severe bronchial spasm which was relieved by one

c.c. of adrenalin. He thereafter passed a comfortable night. The vital capacity determination on the following day, November 1, 1942, was 1,000 c.c., an increase of 300 c.c., or 43 per cent over the pretreatment level.

The same day, November 1, 1942, at 1:30 p.m., he developed a mild asthmatic attack; intravenous oxygen was again administered; the symptoms were relieved; and the oxygen was discontinued after about two hours. At 7:00 p.m. that day, November 1, 1942, moderate wheezing and labored breathing again appeared and intravenous oxygen therapy was resumed. Clinical relief during four hours of therapy was interrupted by a mild attack of asthma and a feeling of precordial distress. Oxygen therapy was discontinued. Because of the precordial distress, further administrations of intravenous oxygen were deemed inadvisable in this patient. The vital capacity determination on the following day, November 2, 1942, was 1,000 c.c. The patient was comfortable until the morning of November 3 when another mild attack was relieved by adrenalin. He was discharged the same day.

During the following three months he had mild daily asthmatic attacks while under treatment at the clinic. After this period his attacks became as frequent and as severe as before the oxygen therapy. The results in this case were unsatisfactory, and any benefit derived might be attributed to bed rest and to the adrenalin injections. However, the oxygen therapy was followed by a period of lessened severity of the asthmatic attacks. The appearance, during the therapy, of precordial distress in this type of patient, in whom a cardiac element was probably of considerable importance, mitigated against further therapy.

In all he received about 4,000 c.c. of oxygen in about 11 hours divided into three periods with a resultant increase in vital capacity of 300 c.c., or 45 per cent above the pretreatment level. This therapy appeared to have had the effect of interrupting the asthmatic attack and of reducing the severity of subsequent attacks for a period of several months.

Case 6. H. K., age 58, was admitted to the allergy clinic on January 25, 1940 with a 15 year history of recurring attacks of coughing, choking, wheezing and difficult breathing throughout the year. During the year prior to the admission to the clinic, the attacks occurred nightly, were associated with intense coughing and profuse expectoration, and were becoming progressively worse. There was also a history of dyspnea on exertion and swelling of the extremities. The family history was negative for allergy.

On examination, the patient showed cyanosis of face, lips and fingers. He had a barrel shaped chest. The heart sounds were poor and distant. Wheezing râles were heard throughout the chest, moist râles and diminished breath sounds at the bases. The blood pressure was 172 mm. Hg systolic and 102 mm. diastolic. The liver was enlarged and there was slight pitting edema of the lower extremities. An electrocardiogram showed slurring of all leads, suggesting myocardial fibrosis. Roentgenographic examination of the chest showed moderate emphysema and a diffuse fibrobronchiectasis. The blood count showed hemoglobin 15 gm., and red blood cells 4,400,000. There were no eosinophiles in the blood smear. The sputum was negative for acid fast bacilli. Roentgenographic examination of the sinuses showed a clouding of the right ethmoid sinus and a veiling of both maxillary antra. Nasal examination showed a marked deviation of the septum and polypoid changes in the mid-turbinates. Skin tests failed to yield any definite reactions beyond a slight to moderate reaction to dust extract.

On the basis of this study, a diagnosis was made of chronic bronchial asthma with bronchiectasis (fibrotic) and of hypertensive heart disease with decompensation. Under therapy with digitalis and mercurial diuretics there was moderate improvement. He continued under observation and treatment with both the cardiac and allergy clinics.

In the allergy clinic he was treated with dust extract and with a stock catarrhal vaccine. Local nasal therapy was also employed. Although he improved slightly, his asthmatic attacks continued. On several occasions, antrum washings revealed frank pus. Infected teeth were extracted. In the course of the following year there was little change in his asthmatic picture, while the cardiac picture varied from time to time under the medical regimen outlined above.

He was admitted to the hospital on November 3, 1942 after attending both the cardiac and allergy clinics for a period of two years without any material improvement. The vital capacity determination on admission was 1,000 c.c.

An electrocardiograph tracing on November 3 suggested right ventricular and auricular hypertrophy. Urinalysis showed specific gravities varying from 1.015 to 1.024, an absence of albumin and sugar and the presence of a trace of acetone. Blood urea was 14.6 mg. Blood pressure was 170 mm. Hg systolic and 90 mm. diastolic. A circulation time determination was not made.

He soon developed difficulty in breathing and wheezing, and intravenous oxygen was begun on November 3 at 6:00 p.m. This therapy was continued throughout the night until 10:00 a.m. November 4. During the night of therapy he had no asthma for the first time in two years. The vital capacity determination on November 4, 1942 was 1,600 c.c., an increase of 600 c.c., or 60 per cent over the pretreatment level.

During the evening of November 4, another attack of difficulty in breathing developed. Intravenous oxygen was again started at 7:00 p.m. and continued until 9:00 a.m. on November 5. During the night of therapy he again was comfortable. The vital capacity determination on November 5, 1942 was 1,800 c.c., a further increase of 200 c.c. over the previous vital capacity. Although no further attack developed, he again received oxygen from 7:00 p.m. on November 5, 1942 to 9:00 a.m. on November 6, 1942. During this interval he again was comfortable. The vital capacity determination on November 6, 1942 was 1,800 c.c., unchanged from the previous level. He was discharged from the hospital November 6, 1942.

On the following day he returned to the clinic and reported that he felt well for the first time in two years. One week later he reported that the improvement had continued, and that he had had but one mild attack of asthma which was relieved by an ephedrine capsule within 15 minutes. He stated that before the oxygen therapy he had had three or four attacks nightly for a long period of time. He could now walk three blocks before any dyspnea developed. On February 3, 1943 he reported that his condition was still improved. A vital capacity determination that day was found to be 1,800 c.c., unchanged from the last level, three months previously.

Gradually his wheezing, shortness of breath and asthmatic attacks returned. On July 15, 1943, the opinion of the cardiologist was that his dyspnea was due mainly to a myocardial insufficiency. Owing to the repeated bouts of cardiac decompensation, it was decided to discontinue clinic treatment and to have him admitted to an institution for chronic diseases. In all he received 22,800 c.c. of oxygen in three days in periods of 14, 14 and 10 hours respectively, with an increase in vital capacity of 800 c.c., or 80 per cent above the pretreatment level.

For a period of three months after this treatment, he was free from asthmatic attacks except for one mild spell noted above.

Case 7. S. K., a tailor, age 53, was admitted to the allergy clinic on January 29, 1941. Following an attack of influenza with a prolonged convalescence 10 years previously, he developed attacks of labored breathing, wheezing and coughing. At first the attacks were infrequent but gradually they became more frequent and more severe. For the two years preceding his first visit to the clinic, he had constant wheezing and shortness of breath. These symptoms were more intense when he was active, but he was not symptom-free even when at rest. He felt somewhat improved during the summer, and worse during the spring and fall. His maternal uncle had asthma.

On examination his face and hands were cyanotic. Nasal examination revealed a deviated septum, enlarged midturbinates, and some mucopurulent discharge in both nasal chambers. The teeth were in poor condition, the gums inflamed. The heart was not enlarged but the sounds were distant and of poor quality. There were many sibilant and sonorous râles throughout both lungs. There was marked emphysema. No evidence of peripheral edema was noted. The sputum was negative for acid fast bacilli.

Roentgenographic examination showed a diffuse fibrobronchiectasis. The heart was of the aortic type. The electrocardiogram showed moderate myocardial damage and auricular enlargement. On test, he showed marked reaction to dust extract and moderate reactions to feathers, dog hair and silk extracts. He reacted only slightly to the pollen extracts.

From February 25, 1941 to June 1942, he was treated specifically with dust, vaccine and ragweed extracts. Treatment with ragweed extract was included because of the onset of symptoms during the fall and a subsequent exacerbation during that season. In June 1942 the antra were washed and a flaky return was obtained. An autogenous vaccine was prepared from this washing and added to the treatment. In September and October 1942, the attacks became more severe and persistent. Intravenous aminophylline gave only temporary relief.

He was admitted to the hospital on November 6, 1942. The vital capacity determination, during a symptom-free interval, was 1,400 c.c. Intravenous oxygen was started at 8:45 p.m. on November 6, 1942 and continued throughout the night until 9:00 a.m. on November 7, 1942. During the night of therapy he was comfortable.

The vital capacity determination on the following day, November 7, 1942, was 1,600 c.c., an increase of 200 c.c., or 14 per cent above the pretreatment level. Intravenous oxygen was again administered from 9:00 p.m. on November 7, 1942 to 10:30 a.m. on November 8, 1942, and again he spent a comfortable night. He continued symptom-free for the next 24 hours, receiving no oxygen during this period and no adrenalin. The vital capacity determination on November 9, 1942 was 1,900 c.c., a further increase of 300 c.c. over the previous level.

For a period of two weeks he continued improved, had no nocturnal asthma, much less dyspnea on exertion, and generally felt better. After this, his cough returned and, within one month, he again was persistently asthmatic, in spite of further specific therapy, penicillin injections and penicillin aerosol. In all he received 9,600 c.c. of oxygen in two days, given in two periods of 12 hours each, with a resultant increase in vital capacity of 500 c.c., or 36 per cent over pretreatment level. Clinical improvement lasted but two weeks.

Case 8. P. C., school girl, age 16, was referred to the allergy clinic on October 17, 1942, after being discharged from the hospital where she had received intravenous oxygen therapy. Her chief complaints were cough, wheezing respiration, difficult breathing and nasal clogging for the past one and one-half years. At the onset, in May 1941, the only complaint was coughing, following a severe upper respiratory infection, but, after February 1942, the cough was associated with attacks of wheezing and difficult breathing. These attacks occurred daily and were relieved by adrenalin injections. There was no seasonal aggravation of symptoms. The family history was negative for allergy.

She was admitted to the hospital on October 9, 1942 for severe and persistent asthma of one month's duration. Examination of the chest revealed typical musical wheezing and whistling râles throughout. The heart was normal; the blood pressure was 128 mm. Hg systolic and 84 mm. diastolic; the blood count showed red blood cells 4,650,000 and a hemoglobin of 90 per cent. The vital capacity determination on admission to the hospital during a free interval was 1,000 c.c.

During the following two days, October 9 and 10, 1942, she coughed at intervals but was fairly comfortable and slept intermittently. At 4:30 a.m. on October 11, 1942 she had a severe asthmatic attack. Intravenous oxygen was started at 5:00 a.m. and was discontinued at 4:30 p.m. that day. During this period she was crying continually, had nausea and headache, but the severity of the asthmatic attack was lessened. At 11:15 p.m. the same day, October 11, 1942, she again had a mild asthmatic attack. Intravenous oxygen was again started but discontinued shortly thereafter as she was very uncoöperative. That night she had some coughing spells but slept at intervals and during the next day, October 12, 1942, she remained fairly comfortable. The vital capacity determination on October 12, 1942 was 1,200 c.c., an increase of 200 c.c., or 20 per cent above the pretreatment level. She was discharged from the hospital on October 12, 1942 stating that she felt considerably relieved, although her wheezing respiration continued as before.

After her discharge from the hospital, she was admitted to the clinic for further treatment on October 17, 1942. There she was tested and showed moderate reactions to dust, feathers and a variety of foods, which were eliminated from her diet. On October 22, 1942, ten days after her oxygen therapy, her attacks were as frequent as before the therapy but less severe and with less cough. In the following week, a mild asthmatic attack occurred which she attributed to the ingestion of cantaloupe and sweet potato, although these foods were negative on skin test. On November 12, 1942, a nasal examination revealed a bilateral, purulent sinusitis, confirmed by roentgen-ray, and involving both ethmoids and both maxillary antra. The roentgenographic examination of the chest revealed a small heart, an accentuation of the root branches, with a general prominence of linear markings. The blood smear showed 8 per cent eosinophiles. The nasal smear showed a predominance of neutrophiles with an occasional eosinophile. The sputum was negative for acid fast bacilli and the urinalysis was negative.

During the following months she was under treatment at the allergy clinic and also in the nose and throat clinic. Frequent bilateral antrum washes revealed purulent returns; her asthmatic attacks continued. A long period of penicillin therapy, both intramuscular and aerosol, yielded but slight improvement at first and later no improvement at all. Radical surgery was resorted to for the infected sinuses with no relief of her symptoms. Subsequent vital capacity studies showed the following:

October 28, 1942: 1,200 c.c.
November 4, 1942: 1,300 c.c.
February 3, 1943: 700 c.c.

In all she received 3,000 c.c. of intravenous oxygen in 12 hours, resulting in an increase in vital capacity of 300 c.c., or 30 per cent, with an immediate slight relief of symptoms during the period of oxygen therapy but with no interruption of her subsequent asthmatic attacks.

This case of bronchial asthma, complicated by a severe paranasal, purulent sinusitis, failed to respond to major sinus surgery on two occasions, to prolonged penicillin therapy, both subcutaneous or aerosol, and to prolonged courses of specific protein therapy. She failed also to respond in any marked degree to the intravenous oxygen therapy. Her attacks have continued severe and recurring throughout the year.

Case 9. B. O., age 44, housewife, with a history of recurring attacks of perennial, bronchial asthma for the past 10 years, was transferred from another institution for the purpose of receiving oxygen therapy. Her attacks came on during the day and night and resisted all forms of medication. In addition she was very emotional and neurotic. There was no allergy study in this case prior to her admission to the hospital.

On admission, the vital capacity determination on October 21, 1942 was 1,800 c.c. Intravenous oxygen was started on October 21, 1942 at 7:30 p.m. but was discontinued at 8:00 p.m. because of severity of the dyspnea and the complete lack of coöperation. Adrenalin yielded only slight temporary relief. During the night she was restless, and moaning and crying frequently. She was very emotional and apprehensive.

On the following day, October 22, 1942, she had a mild asthmatic attack. On examination there were many sibilant and sonorous râles throughout both lungs. Intravenous oxygen was started at 5:15 p.m. and the patient felt a general bodily warmth within five minutes with some relief of the bronchospasm. She objected to the needle in the vein, attempting to pull it out repeatedly and the oxygen was discontinued after two hours, at 7:15 p.m. Thereafter she passed a comfortable night, sleeping at intervals, and also passed a comfortable day. At 8:00 p.m. on the following day, October 23, intravenous oxygen was again started but was discontinued after one hour, again because of her emotional state. The vital capacity determination, on October 24, 1942, was 1,900 c.c., an increase of 100 c.c., or 6 per cent over the pretreatment level.

On October 25, 1942 she had several attacks of difficulty in breathing and complained of pains in the chest and cardiac region. Intravenous oxygen was started at 7:45 p.m. and discontinued in five minutes as the patient was very restless, complaining of precordial distress and difficulty in breathing. The vital capacity determination on October 26, 1942 was 1,800 c.c., back to the pretreatment level. She was discharged by ambulance to her own institution on October 26 after refusing further treatment.

Owing to the lack of coöperation and to the emotional state of the patient, oxygen was administered in short intervals with very little effect on either the vital capacity or the frequency of the asthmatic attacks. In all she received 800 c.c. of oxygen with an increase in vital capacity of 100 c.c., or 6 per cent, which was not sustained and may have been within the range of technical error.

Results and Discussions

Intravenous oxygen therapy was administered in amounts ranging from 3,000 c.c. to 22,000 c.c. in one, two or three stages, in a series of nine cases of severe and persistent bronchial asthma, usually after the onset of an attack. The results in case 9 are not included as the patient was emotional and did not coöperate. The following effects were noted:

1. On vital capacity: Following the therapy, the vital capacities in all cases were increased in amounts ranging from 300 c.c., or 30 per cent, to 1,300 c.c., or 87 per cent. This increase was maintained in five cases after one month and in one case after three months. In two cases, subsequent determinations were not made. This increase in vital capacity was lost after three months in three cases and in two cases fell below pretreatment levels in four months and eight months respectively.

2. On clinical symptoms: In all cases, there was some degree of immediate relief of clinical symptoms, appearing within five minutes to two hours of the beginning of the therapy. This was evidenced by a very definite lessening of the dyspnea, wheezing respiration and respiratory effort. In four cases a feeling of general bodily warmth developed immediately after the beginning of the therapy. The duration of the clinical improvement varied roughly with the total amounts of oxygen administered. In two

cases, receiving the smallest amounts of oxygen, 3,000 c.c. and 4,000 c.c. respectively, there was a recurrence of all symptoms within 10 days, following only slight immediate improvement. In one case, receiving 9,600 c.c. of oxygen with immediate relief of symptoms, there was a recurrence after one month. In the five remaining cases, receiving from 8,000 c.c. to 22,000 c.c. of oxygen with immediate relief, the clinical improvement was maintained for four to six months. Of this latter group, one was asthma-free for four months and the others had one to two attacks in six months. Several of these attacks were traced to the ingestion of fish and contact with excessive amounts of dust. In all cases but one, the asthmatic attacks returned to pretreatment intensity after six months.

Two cases in this series had exceptionally low initial vital capacities. In one, after 22,000 c.c. of intravenous oxygen, the initial vital capacity of 1,000 c.c. was increased 80 per cent to 1,800 c.c. and was maintained at this level for three months with an absence of asthmatic attacks for four months. In the other, after 9,000 c.c. of intravenous oxygen, the initial vital capacity of 800 c.c. was increased 87 per cent to 1,500 c.c. and was maintained at this level for one month with but one attack of asthma for six months, at the end of which time the vital capacity had returned to a level of 25 per cent above the pretreatment vital capacity.

In the cases presented in this report, the intravenous administration of oxygen to these severe asthmatics yielded prompt relief from the asthmatic paroxysms. Also, there occurred a prompt increase in vital capacities in all cases. These increases persisted after such administrations for periods up to three months and relief of symptoms generally extended beyond the period of increased vital capacity, despite the absence of further such oxygen administration.

Previous investigators have noted that the beneficial results after intravenous oxygen were more permanent than apparently could be explained by the mere relief of cyanosis [2b] and that the improvement in patients seemed to be out of all proportion to the small amounts of oxygen so administered.[3] These facts were noted also in our series of cases. The absence of untoward incidents was believed due to the slow administration and to the low pressure of the flow of oxygen. There is a possibility that the effect of intravenously administered oxygen in asthma was due to an action of the oxygen other than that of relieving an existing anoxemia alone. However, whether or not oxygen so administered acts therapeutically in a manner different from oxygen administered by inhalation can only be conjectured at this time.

More extensive data on various fundamental physiologic effects of intravenous oxygen are needed than the literature presently extant contains. Such investigations must await an apparatus more sensitive and self-regulatory than is yet available.

Summary

1. Intravenous oxygen was administered to a series of nine cases of severe bronchial asthma, generally following the onset of an attack.

2. As a result, there was a remission of symptoms immediately in eight cases, lasting from 10 days to six months.

3. There resulted an increase in vital capacities in all cases of from 30 per cent to 87 per cent depending roughly on the amounts of oxygen administered. This increase was lost after three months and fell below pretreatment levels in two cases within eight months.

4. The maintenance of clinical improvement generally extended beyond the period of the maintenance of the increased vital capacity.

5. Very low vital capacities, when sufficiently increased following the intravenous oxygen therapy, yielded beneficial results, even though the resulting vital capacities were still greatly below normal.

6. Whether or not intravenously injected oxygen acts therapeutically in a manner similar to inhaled oxygen can only be conjectured at this time.

We should like to express our thanks to Miss Elsie Kaye, of the department of pathology, for the vital capacity determinations recorded in this study, so painstakingly and patiently performed upon subjects often recalcitrant. We should also like to extend our thanks to Drs. Rothman, Hotkin and Kravchick, of the interne staff, for their coöperation in observing these patients over extended periods during the oxygen administration.

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PATHOGENESIS OF COCCIDIOIDOMYCOSIS WITH SPECIAL REFERENCE TO PULMONARY CAVITATION *

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IT is now accepted that human infections of *Coccidioides immitis* are usually acquired by inhaling the chlamydospores and arthrospores of the fungus. Occasionally the portal of entry may be by abrasions or lacerations.[8] After an incubation period ranging from one to three weeks, symptoms develop in approximately 40 per cent of infected males.[37] However, three-fifths of the infections are completely asymptomatic. The pneumonic or respiratory symptoms which occur in two-fifths are of varying degrees of severity. Among females an increased frequency of erythema nodosum results in a somewhat higher proportion of clinically manifest disease. This erythema nodosum is a complication of the initial infection associated with the hypersensitive state.[10, 35, 38] It occurs in 4 per cent of all coccidioidal infections of white males and one-fifth of their clinically manifest disease.[37] Among adult females it is found in 10 to 25 per cent of their infections and 40 per cent of their clinically manifest disease. Pleural effusion is another occasional complication which occurs relatively soon after the infection is acquired. Even though the fungus is usually recoverable from the pleural fluid, the infection is rarely progressive. A third complication of the primary infection may be pulmonary cavitation and even spontaneous pneumothorax or hydropneumothorax. These complications will be the principal subject of this paper. There continues to be considerable confusion between them and the progressive or disseminating form of infection, coccidioidal granuloma. It is our wish to aid in this clarification and to provide help in distinguishing coccidioidal cavitation from tuberculosis.

Coccidioidal granuloma or disseminated, progressive, or secondary coccidioidal infection, was the only form recognized until Gifford [14] and Dickson [9] reported that *Coccidioides* is the cause of benign "Valley Fever." Its

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From the Commission on Acute Respiratory Diseases, Army Epidemiological Board, Office of the Surgeon General, Department of the Army, and its project for the study of coccidioidomycosis in the Department of Public Health and Preventive Medicine, Stanford University School of Medicine, San Francisco, California. Preliminary studies 1937–1941 were supported by the Rosenberg Foundation.

The data presented are the result of coöperative effort. We cannot express adequately our gratitude even to the extent of listing all who provided histories and replied to our many inquiries. However, in the military hospitals we are especially indebted to Col. Hugh W. Mahon and his colleagues at Fitzsimons General Hospital. Among the civilians the following physicians provided especial aid: W. A. Winn, R. H. Smart, S. L. Goldman, M. A. Gifford and E. Bogen. Appreciation for notable specific collaboration of others is also indicated at the appropriate points of the text.

clinical manifestations are well known: extrapulmonary lesions of lymph nodes, bones, joints, central nervous system, peritoneum, genital tract, skin, mucous membranes of the mouth, indeed, of all organs and of all degrees of severity. The mimicry of extrapulmonary tuberculosis is notorious, as is the 50 per cent case fatality. The military studies [37] have shown that among white adult males approximately 1 in 380 of those infected and 1 in 100 with clinical disease undergo extrapulmonary dissemination. Among Negro adult males the risk of dissemination is at least 10 times as great.[22, 37] Dissemination is much less frequent in females.[2, 15] Army experience [22, 23, 37] also has indicated that dissemination usually occurs soon after the infection is acquired, frequently within a matter of weeks and infrequently after months. It rarely occurs in the second year after the infection, although a few cases are seen. Once dissemination ensues, the risk of continued dissemination is

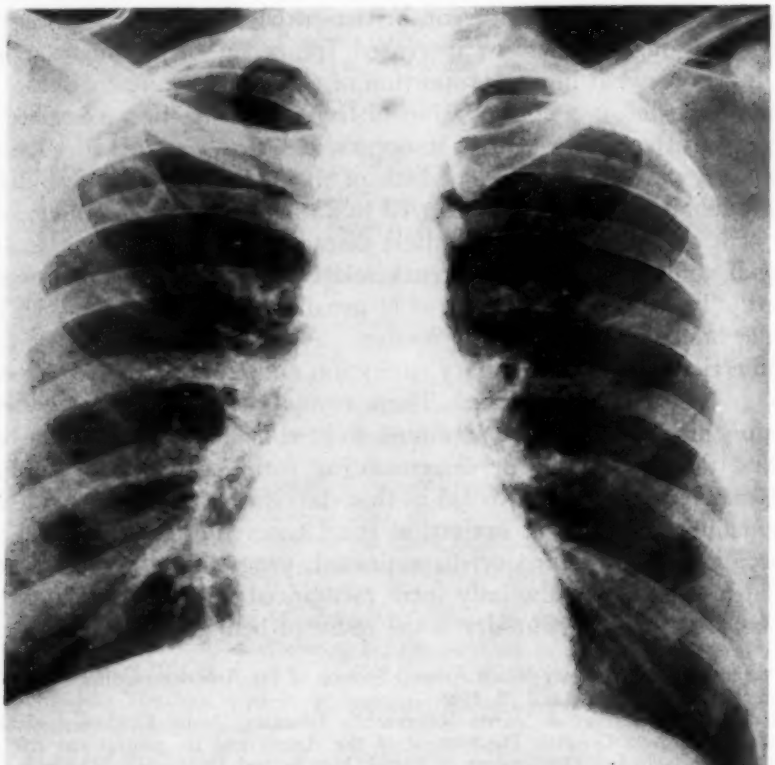

FIG. 1A.

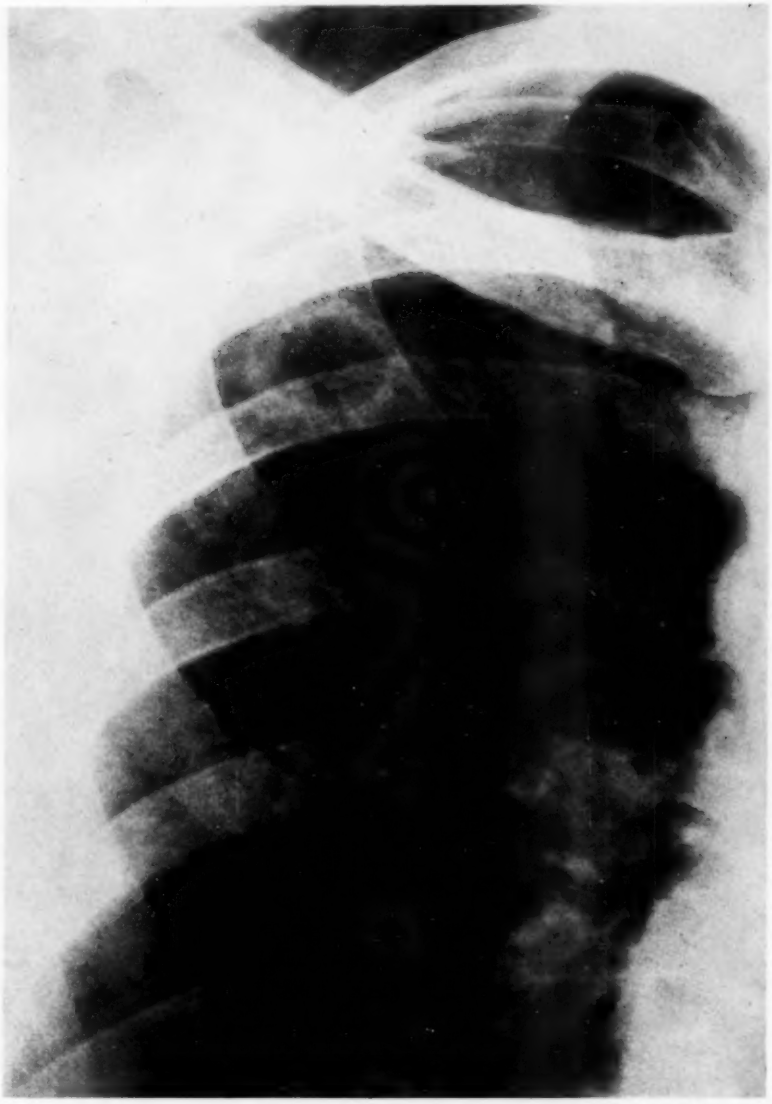

FIG. 1B.

FIG. 1. A and B. Coccidioidal cavity detected in routine coccidioidin survey. Coccidioidin tests negative July 1941 and June 1942 but positive in August 1943. History of malaise, respiratory illness and transient chest pain September 1942. Roentgenogram September 10, 1943, shows cavity in periphery RUL under second rib. *Coccidioides* recovered from sputum. Serology entirely negative. Cavity closed and reopened several times, finally closing permanently November 1944.

great even though remission may occur. Autopsies of those dying of disseminated infections may show lesions of varying periods and lead to the deduction that late disseminations are frequent.[13] However, those observations do not take into account this continued vulnerability of the immuno-

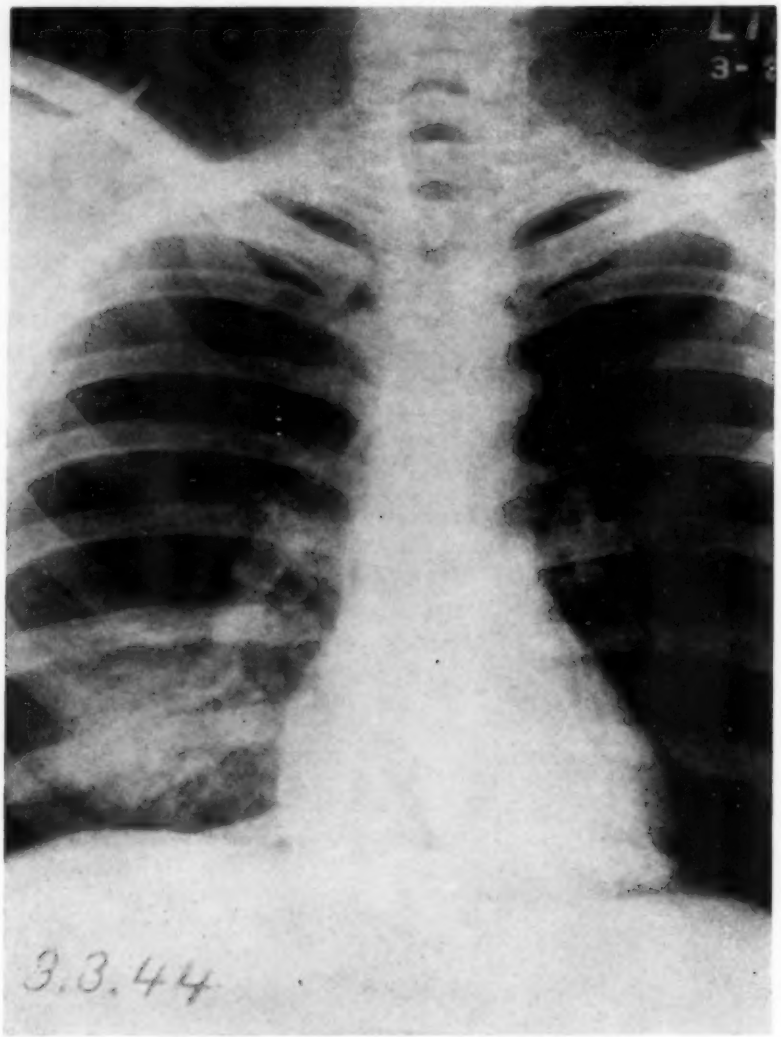

FIG. 2A (i).

logically defective. Among those of us who have handled our infections satisfactorily, the chance of late disseminations is negligible. These statements sound dogmatic and it is regrettable that we do not have time to develop them adequately. We do point out that *none* of our military coccidioidal patients, of whom we had records of thousands, has ever been reported to us as having undergone a postwar dissemination. Furthermore, none of the many thousands of service men who were coccidioidin reactors when given their routine test on arrival at their stations was ever known to have undergone dissemination. Disseminations occurred only in those who arrived uninfected, acquired infection and then disseminated. We reiterate

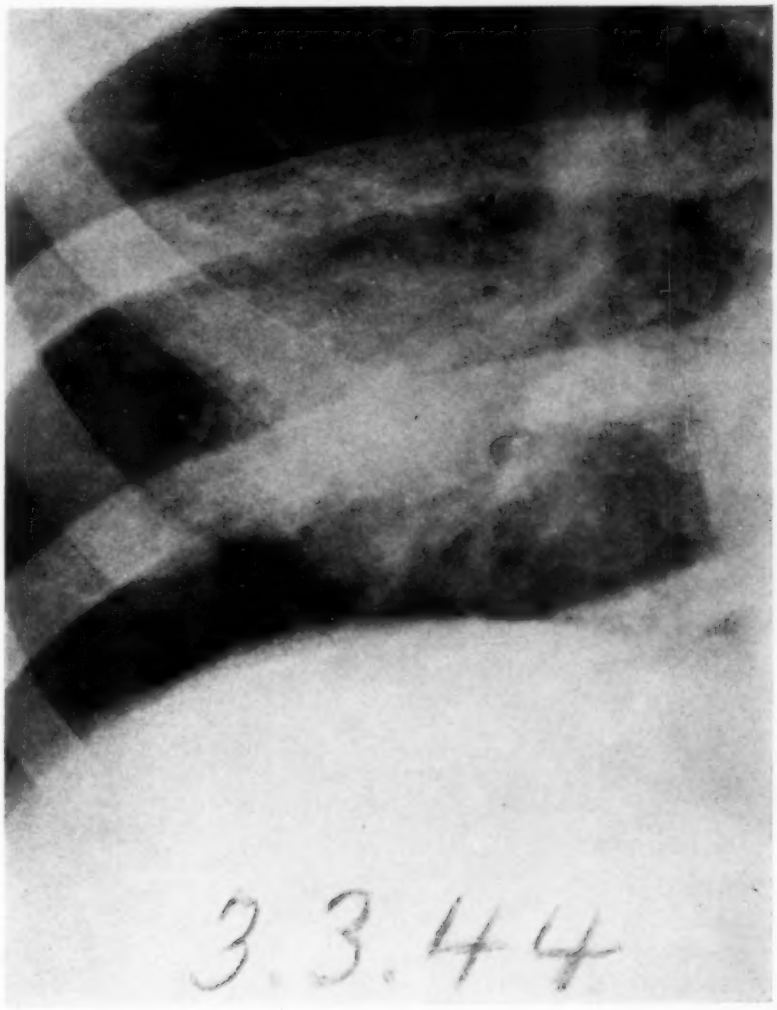

FIG. 2A (ii).

that coccidioidal pulmonary cavitation is not in the category of disseminating or progressive coccidioidal granuloma.

Coccidioidal pulmonary cavitation, first reported in isolated instances by Farness and Mills [11] and Yegian and Kegel [44] and then so excellently described by Winn,[41] is now familiar to us all. The thin wall with little reaction around (figure 1, figure 5A) may cause confusion with lung cysts. Indeed, in recently reviewing our correspondence with Winn, we were interested to see the earnestness with which we discussed whether his cases were cysts with *Coccidioides* implanted or due entirely to the coccidioidal infection. Their very force of numbers drove us to the latter conclusion. The first lobectomy treatment for this condition which is known to us was per-

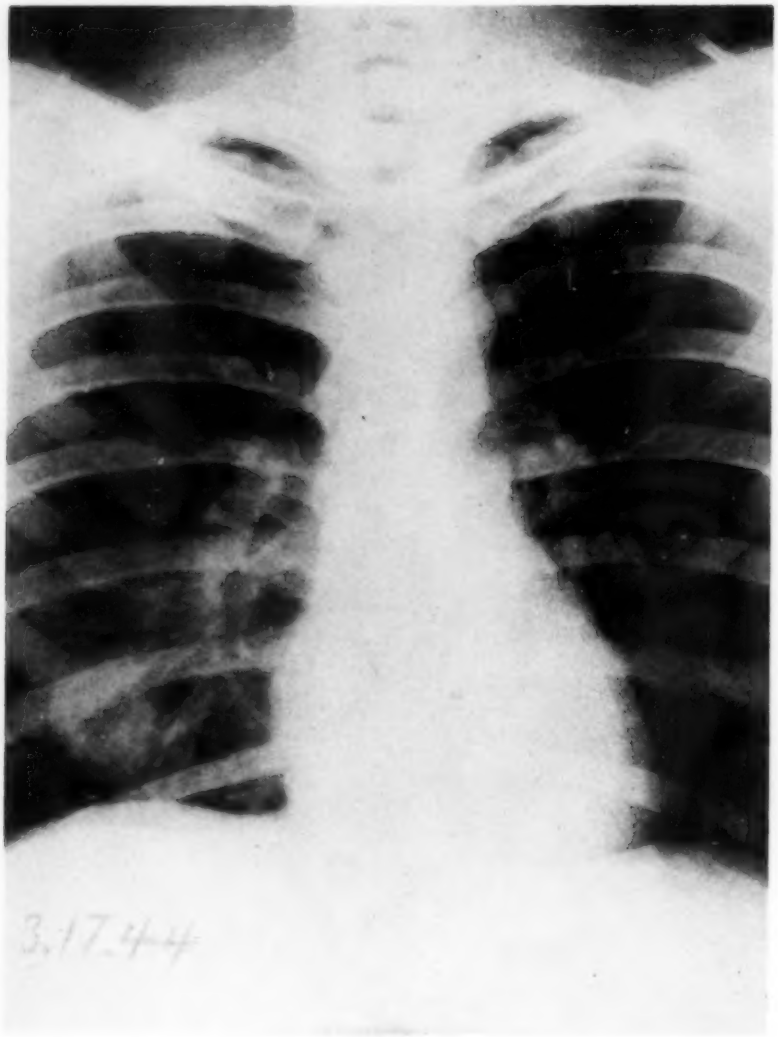

FIG. 2B (i).

formed by Brunn who described his patient as having lung cysts.[3] The descriptions of Powers and Starks [28] and of Colburn [6] of cavity formation in the acute coccidioidal illness were greatly extended by Sweigert, Turner and Gillespie [39] in their military cases. The most extensive roentgenographic descriptions have been by Jamison [18] and by Jamison and Carter [19] in their presentation of the cavity cases originating in the Western Flying Training Command. There is general agreement that cavities may develop early in the course of the primary illness, often beginning within the pneumonic lesion in a week or two of the onset (figures 2 and 3). On the other hand, the single or multiple pneumonic areas may reduce in size to nodular or irregular

FIG. 2B (ii).

residuals over a period of weeks or months. The patient may be completely over his clinical illness with sedimentation rate normal and serologic tests waning. Then an excavation may develop and a cavity rapidly form. We are not qualified to discuss the mechanism by which these cavities develop and would refer you to papers indicated above.[6, 18, 19, 39, 41] From the immunologic point of view, in only very rare cases is the infection seriously active. We have never seen dissemination occur in a patient with coccidioidal cavitation. Recently Kurz and Loud [21] have reported one, a very unusual case. The patient's pulmonary roentgenogram showed a thin walled solitary cavity which certainly "looked coccidioidal," although no mention was made of whether *Coccidioides* was recovered from the sputum.

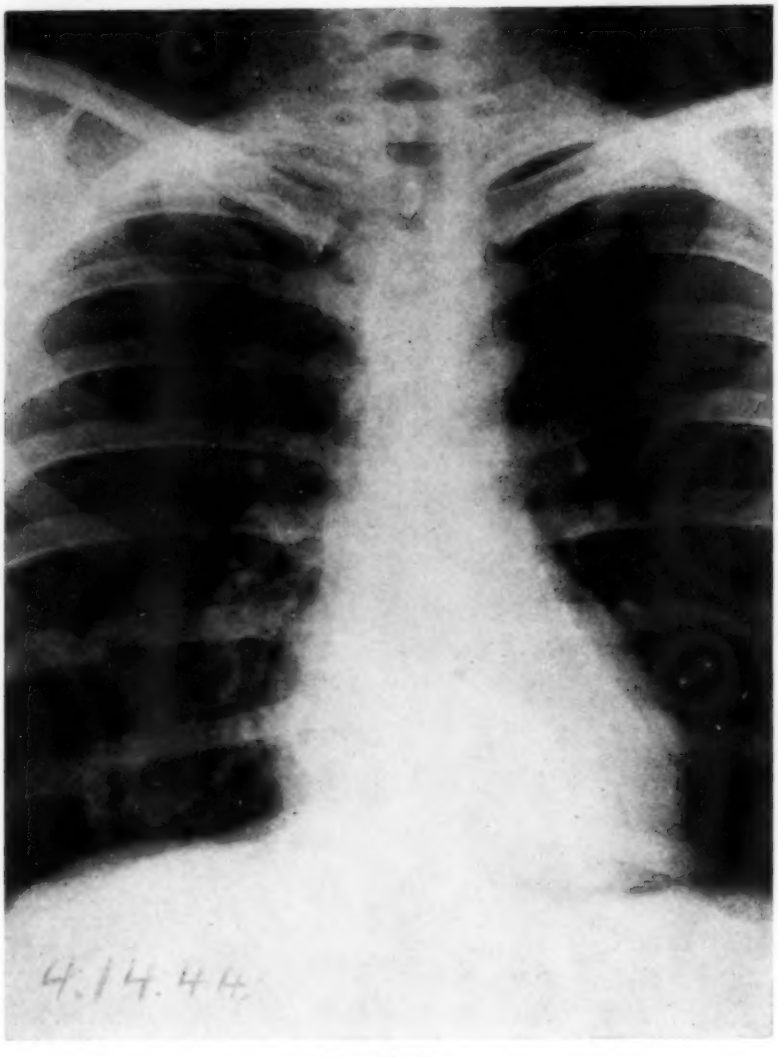

FIG. 2C (i).

Within the second year after he had been stationed in a coccidioidal endemic area, trauma resulted in a facial lesion confirmed by biopsy as coccidioidal. Under heavy roentgen therapy it healed completely. Even while the facial lesion was active, the sedimentation rate was only 4 mm. Dr. Reginald Smart [34] informs us of one patient known by him to have had a coccidioidal cavity who died of coccidioidal meningitis. The nearest approach to progressive disease in our series is the case of a Negro dining car worker, a patient of Dr. Smart.[34] He had very extensive cavitation in both lungs with recovery of the fungus from the sputum. The lesions in the lungs were described as progressing. His serum fixed complement in a dilution

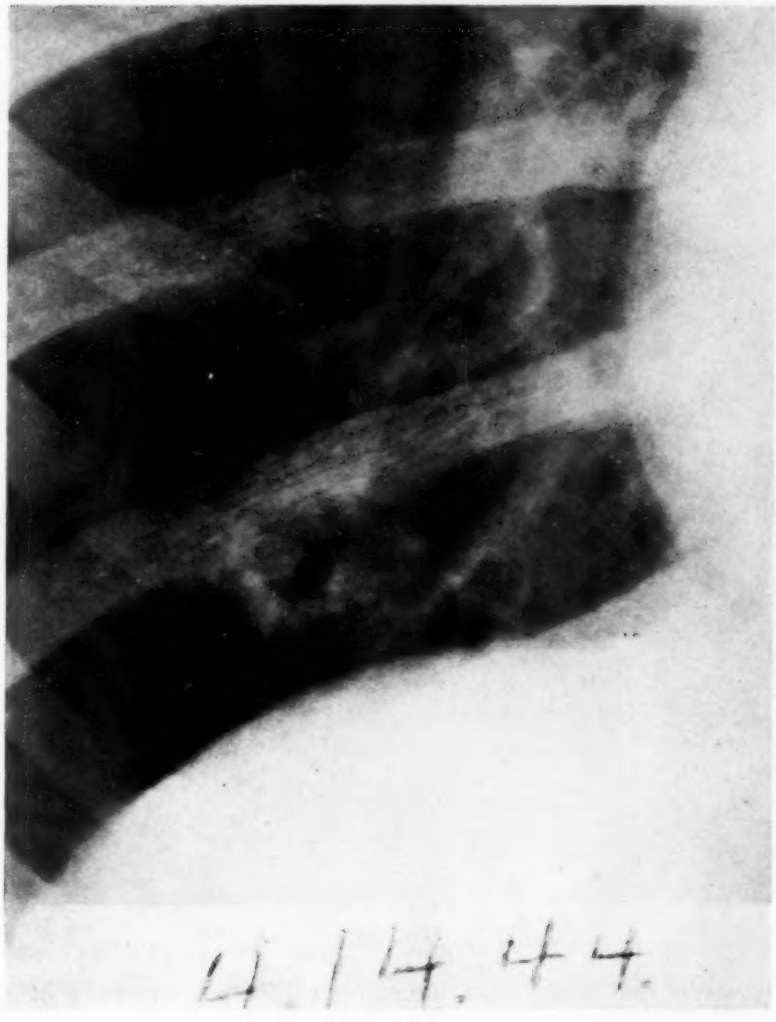

FIG. 2C (ii).

FIG. 2. Development of coccidioidal cavity in area of pneumonitis. Recovery of *Coccidioides* from sputum. Positive precipitins and complement fixation. Conversion of coccidioidin.

A. Infiltration in right base three days after onset. Sedimentation rate 25 mm.
B. Beginning cavitation two weeks later. Sedimentation rate 19 mm.
C. Fully developed cavity six weeks after onset. Sedimentation rate 4 mm.
Cavity persisted eight months, closed and reopened several times but after a year remained closed permanently.

of 1:64. His sedimentation rate was very rapid. However, he had no extrapulmonary lesions and when last heard from in 1945, seven years after diagnosis, was still alive. One patient with coccidioidal cavitation was suspected by Dr. Smart as having undergone a bronchogenic spread although his serum complement fixation held at only 1:4. However, he was debili-

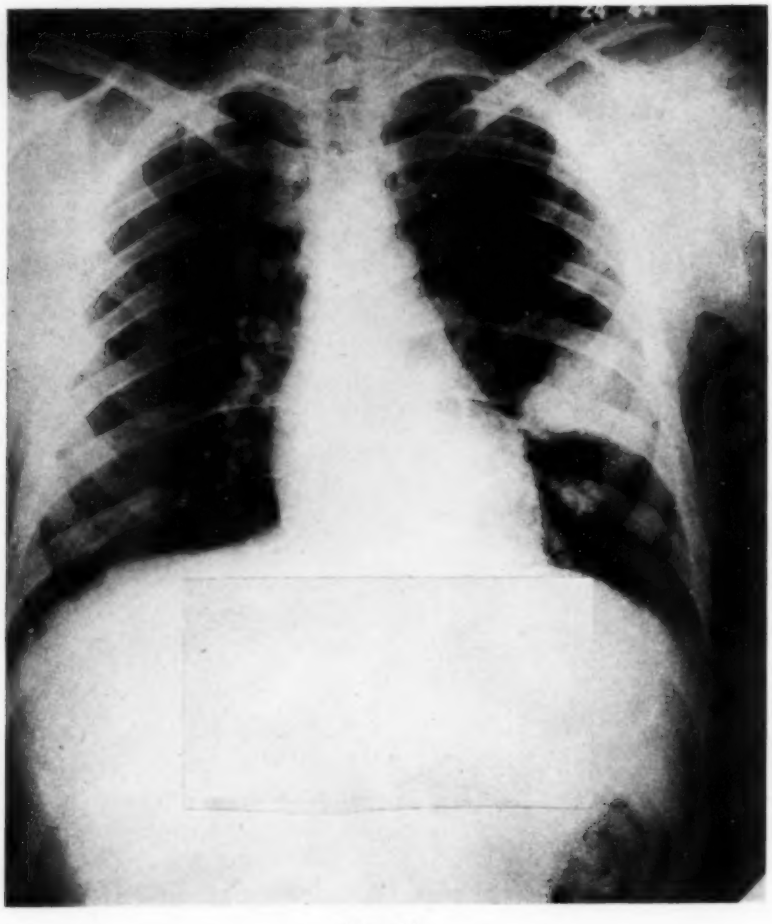

FIG. 3A.

tated by severe and progressive ulcerative colitis. After death in another city, no autopsy was performed. It is apparent that these are unusual cases with complicating features. The consensus of those who have observed both coccidioidal cavitations and disseminations as major complications of the initial coccidioidal infection was aptly phrased by the former Chief of Professional Services at Santa Ana, Dr. George Houck, when he said [17] "While we did not enthuse at the prospect of a patient's prolonged hospitalization, his cavity formation allayed any apprehension of dissemination."

It has been possible to accumulate reasonably accurate data on frequency of dissemination of coccidioidal infection.[37] Estimating the incidence of pulmonary cavitation is much more difficult. The cavity may appear transiently during the acute infection and thus be missed. The cavity may develop months after the acute infection is over, as detection during routine Army roentgenograms showed (figure 4). Thus the association with the

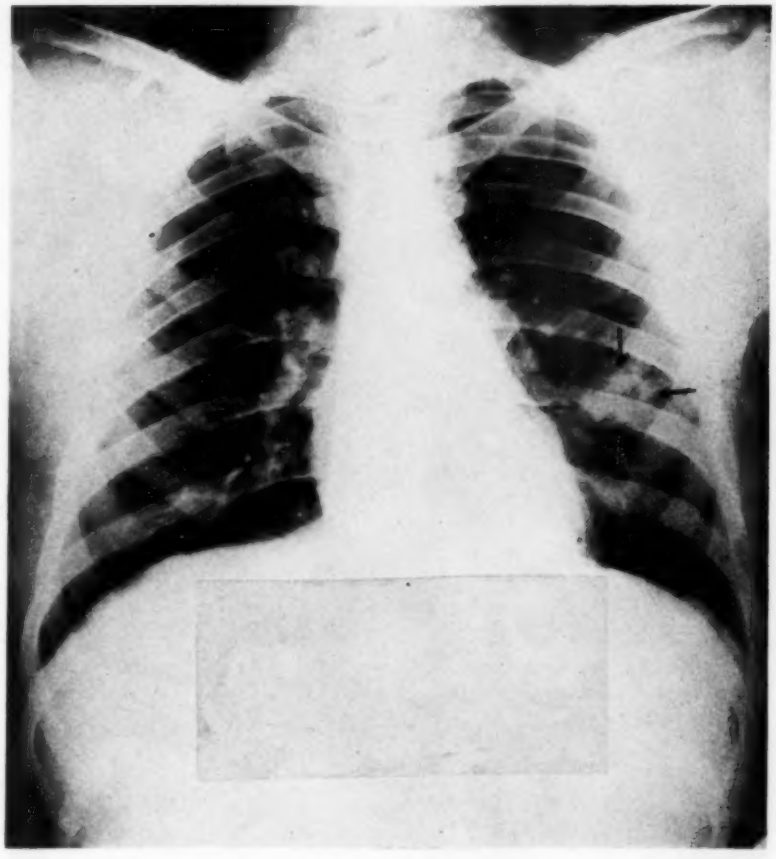

FIG. 3B.

initial infection is readily overlooked. Moreover, cavities may develop after completely inapparent infection. As we shall see, few cavities produce sufficient symptoms to warrant consulting a physician and his ordering a roentgenogram. In the following four studies the frequency of cavitation in clinically manifest primary infection has been calculated. In a study of 77 coccidioidal patients hospitalized at Davis-Monthan Field, Swiegert, Turner and Gillespie [39] reported cavitation in 6 or 8 per cent. Willett and Weiss [40] described cavities in six of 100 coccidioidal patients hospitalized at March Field. Colburn [6] and Goldstein and Louie [16] reported three cavities (4 per cent) in the 75 cases at Camp San Luis Obispo. In our 753 cases of coccidioidal disease hospitalized at Minter, Gardner, Lemoore and Merced Army Air Fields, cavities were detected in 13 or 1.7 per cent.[31] It should be emphasized that these figures apply only to the 25 to 40 per cent of the infections with manifest symptoms. Incidence of cavitation in inapparent infections cannot be estimated. When one recalls the handicaps in the recognition of coccidioidal cavitation, it is very apparent that this complication

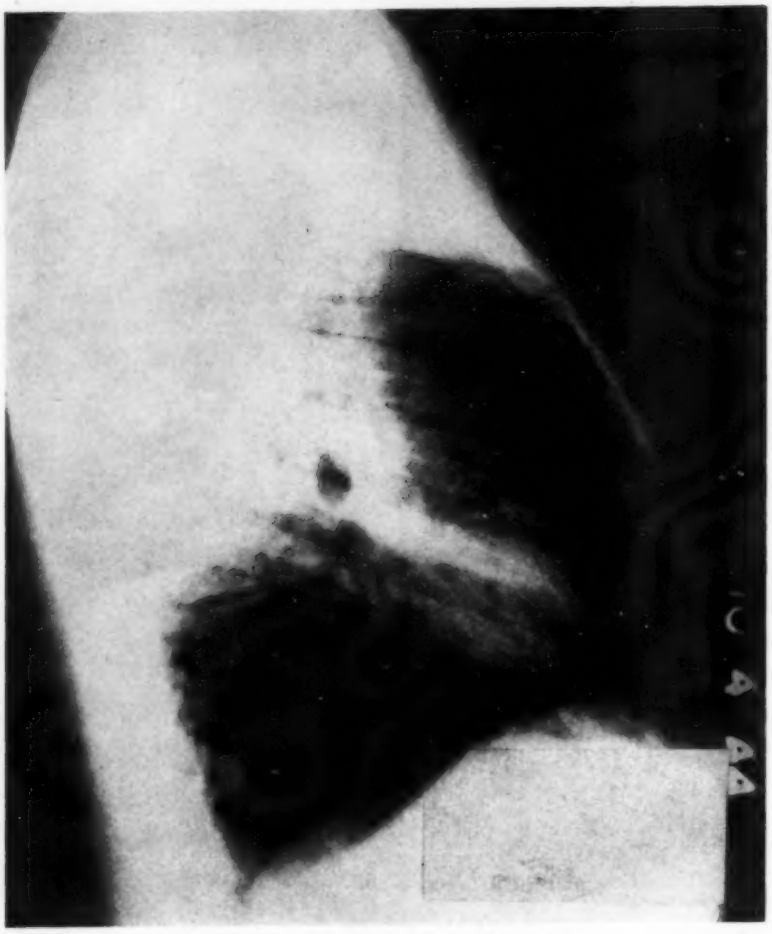

FIG. 3C.

is much more frequent than is dissemination. Fortunately, pulmonary cavitation is relatively benign.

Our files contain records of 274 patients with pulmonary cavities which undoubtedly are coccidioidal. One criterion for the coccidioidal etiology was recovery of the fungus (proved culturally and by animal inoculations,[26]

TABLE I

Criteria by Which Coccidioidal Etiology Was Diagnosed on 274 Patients with Pulmonary Cavitation

	No.	%
Cultures positive	109	(40)
Serology positive (cultures negative or not made)	134	(49)
Coccidioidin positive, tuberculin negative (cultures negative or not made; serology negative or equivocal)	31	(11)
	274	(100)

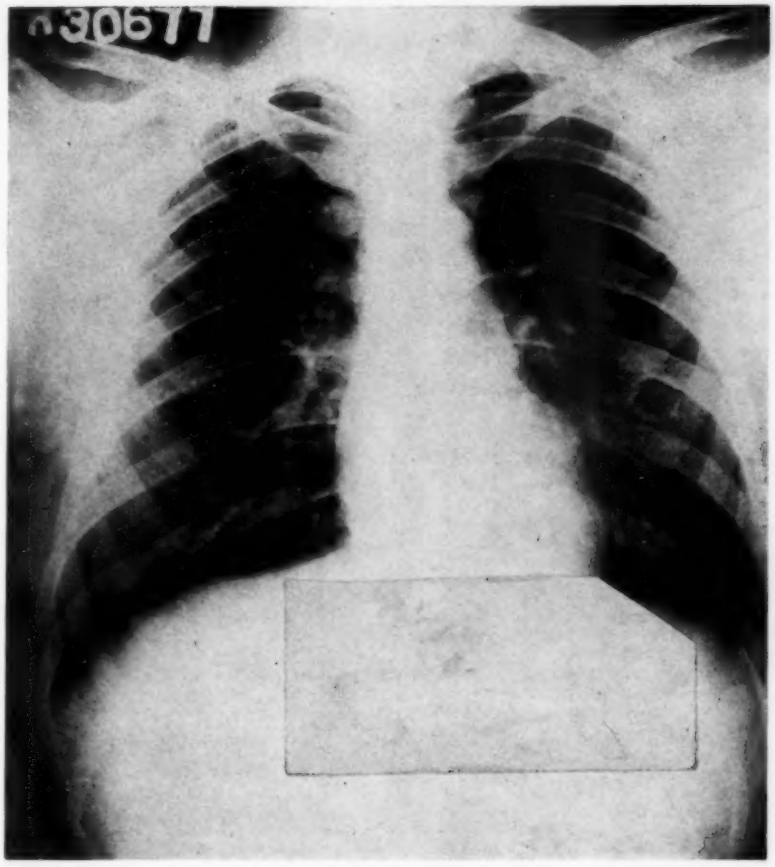

FIG. 3C (i).

not by undependable coverslip examination of sputum) (table 1). A second acceptable criterion was demonstration of positive serology, precipitins during the acute phase or complete fixation of complement in at least the first (1:2) dilution of serum. The third acceptable group had positive coccidioidin and negative tuberculin tests. Even though the cavity looked "typical" and the patient had a positive coccidioidin reaction and partial complement fixation, if his tuberculin test was positive or was never performed, he was not included. We excluded 87 patients whose cavities were reported to be coccidioidal but who could not meet these standards. It must be admitted that we ourselves did not see the roentgenograms of most of these patients and had to depend on the opinion of others. We excluded all in which there was any expression of doubt, such as "emphysematous bleb" or *"possible cavity."* Of the 169 from military and veterans hospitals 128 were from General and Regional Hospitals and 15 from Veterans Hospitals. The Chief of Professional Service at the Santa Ana Army Air

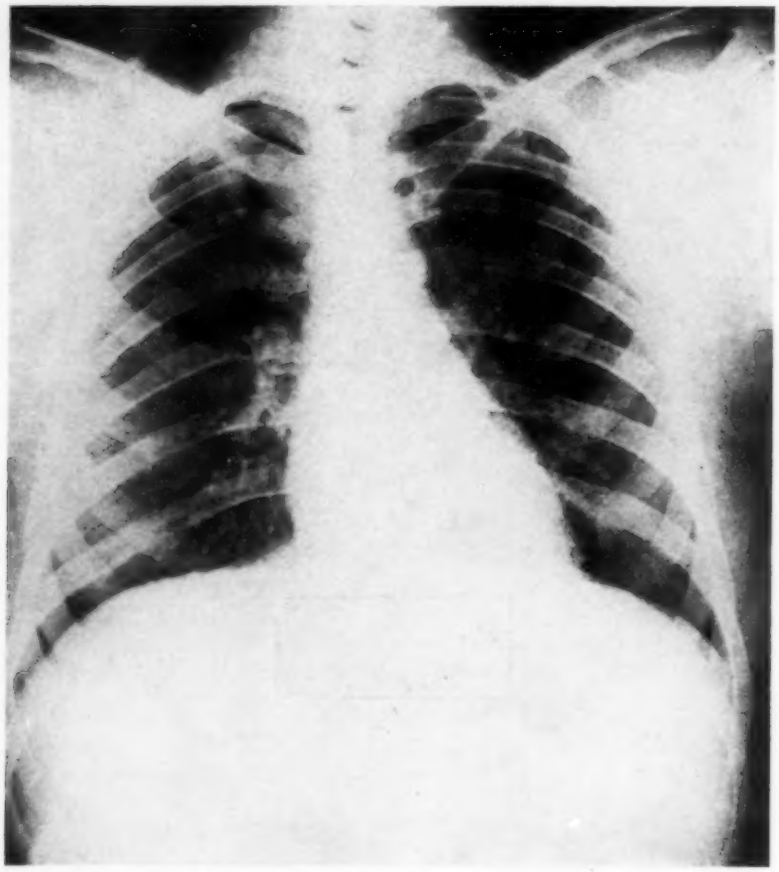

FIG. 3D.

FIG. 3. Development of coccidioidal cavity in residual nummular area and eventual disappearance. No sputum studies made. Complement fixed through 1:4 serum dilution; precipitins present initially. Conversion of coccidioidin skin test.

A. Pneumonic lesion in left lower lung two days after onset. Sedimentation rate 18 mm.
B. Resolution of infiltration to residual nummular lesion but beginning cavity formation 25 days after onset. Sedimentation rate 9 mm.
C. Well-defined cavity 2½ months after onset. Sedimentation rate "normal." (i) Anterior-posterior view. (ii) Lateral view.
Cavity continued clearly defined for six months, then less sharply outlined.
D. Lung clear one year after onset. Sedimentation rate 4 mm.

Lung still clear two years later and sedimentation rate 4 mm. However, complement still fixed through 1:4 dilution, the same titer as at onset.

Base [17] has declared that in his experience the coccidioidal cavities were never "over-read" but the errors of the stations hospitals of the Western Flying Training Command which "fed" into Santa Ana were in overlooking them. Of the 105 cavities observed in civilians, 92 were diagnosed by recognized phthisiologists. Some of these cavities may have been "phantom," but when we note that 89 per cent of the etiological diagnoses were based on cultures

or serology, the coccidioidal mischief is clear-cut. An occasional bronchiectatic focus might account for a positive sputum, but this complication is much rarer than cavitation.

A possible pitfall in diagnosing the etiology of cavitation may be infection with both *M. tuberculosis* and *C. immitis*. Proof of one infection may terminate studies which would have revealed the other, too. Double infections have been reported in three patients by Cherry and Bartlett [4] and in a patient with spontaneous hydropneumothorax by Rifkin, Feldman, Hawes and Gordon.[29] Included in our group are seven more double infections. Both organisms were recovered from five. In the other two, *M. tuberculosis* was recovered and the rôle of *Coccidioides* was indicated by fixation of serum to a diagnostic titer. Whether persistent search for *Coccidioides* would have revealed the fungus also, we cannot say. In only one of these cases, a Negro reported by Dr. W. L. Nalls [26] at the Oteen, N. C., Veterans Hospital, did the tuberculous infection appear to be progressive. In no instance did the coccidioidal infection progress. Certainly coccidioidal infections rarely "activate" a quiescent tuberculous infection. In only one of 753 patients hospitalized with coccidioidomycosis [31] did we discover active clinical tuberculosis. On one occasion we visited a military hospital located in such a highly endemic coccidioidal area that 50 per cent of the susceptibles stationed in the region acquired coccidioidal infections within six months. Because of the dry warm climate, tuberculous patients were being brought in for treatment. Although their only exposures were in the hospital wards, we discovered that 11 had acquired coccidioidal infections. Ubiquitous desert dust supplied the infecting chlamydospores. In none of the 11 was the coccidioidal infection especially severe, though one did develop a coccidioidal effusion on the side opposite that in which had appeared the tuberculous effusion which necessitated his hospitalization. The clinicians caring for the patients stated that the coccidioidal infections had not hampered the healing of the tuberculosis. However, we may note that coccidioidal pulmonary cavitation does not preclude active tuberculosis or vice versa.

Our data do not permit an adequate analysis of the symptoms associated with pulmonary cavitation. However, in 224 of the 274 we are able to present the reason why the roentgenogram was taken which revealed the lesion. In table 2 we observe that in nearly three-fifths of the military group these were routine films. In 25 the routine films were made on separation from the service; in four of the 12 "incidental illnesses" the pictures were taken in the course of the chest surveys of the wounded. These findings bespeak the characteristically "silent" character of these lesions. One notes that in the civilian group only one-quarter were detected as "silent" lesions. Of course this is not because of the more severe nature of lesions in civilians but because roentgenograms are much less frequently taken. This point is further borne out by the fact that the proportion of the coccidioidal

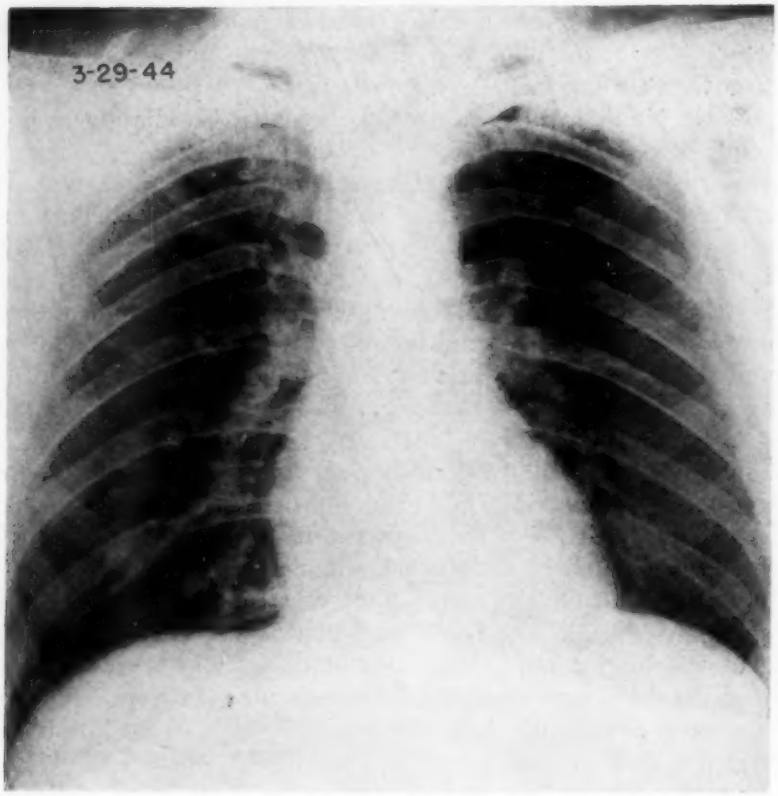

FIG. 4A.

cavities detected in the course of clinical illness was twice as high in the military as in the civilian group. One notes that the outstanding sign or symptom produced by the cavitation was hemoptysis. Nearly three-fifths of the civilian group were detected because of that danger sign. It was

TABLE II

Reasons for Taking Roentgenograms Which Resulted in 224 Diagnoses of Coccidioidal Pulmonary Cavitations

	Military			Civilian		
	No.	(%)		No.	(%)	
Routine (no illness)	73	(48)		14	(20)	
For another illness	12	(8)		3	(4)	
Coccidioidin survey	3	(2)		0		
Total incidental discoveries	88		(58)	17		(24)
Hemoptysis	24	(15)		40	(57)	
Chest pain	9	(6)		2	(3)	
Cough, malaise, fever or sputum	6	(4)		6	(8)	
Course of acute coccidioidomycosis	26	(17)		6	(8)	
Total with specific symptoms	65		(42)	54		(76)
ALL	153	(100)		71	(100)	

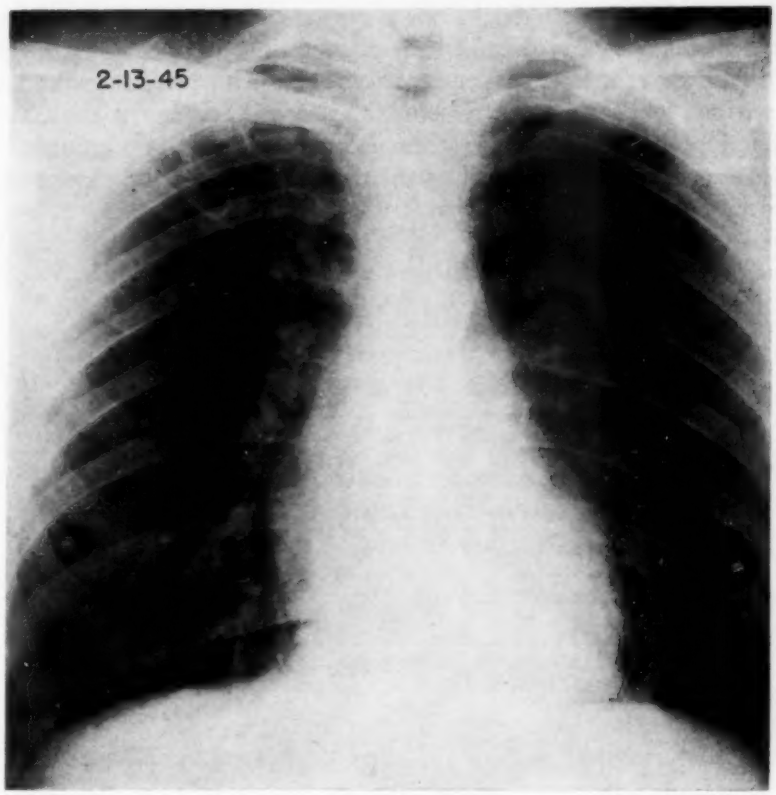

FIG. 4B.

FIG. 4. Development of multilocular cavity from infiltration accompanying asymptomatic infection. *Coccidioides* constantly recoverable from sputum. Complement fixation through 1:8 serum dilution. Positive coccidioidin test. Sedimentation rate consistently normal.

A. Routine survey roentgenogram to qualify for overseas service. Extensive infiltration right apex with negative tuberculin. No preceding symptoms. Despite prolonged bed rest cavities gradually developed.

B. Multilocular cavities present in site of old infiltration 11 months later. Sedimentation rate still normal.

Subsequently developed considerable sputum and frequent hemoptysis. Two years after diagnosis complement fixed 1:32. Lobectomy 1948.

rarely sufficient to menace health, but was often so frequent and alarming as to make the victim unemployable. Chest pain, cough, malaise, fever or excessive sputum accounted for only one-tenth of the military and civilian discoveries. Thus the benign clinical nature of most coccidioidal pulmonary cavities is notable. They are in marked contrast to the fever, malaise, asthenia and severity of the illness observed in disseminated coccidioidal infection (coccidioidal granuloma).

In 269 we could note the number of cavities. While a solitary cavity is "characteristic," multiple coccidioidal cavities do occur. As table 3 indi-

cates, nine-tenths were single. Four per cent were multilocular (figure 4). As noted in table 4, there seemed no outstanding predilection for right or left side (45 per cent left; 55 per cent right). With respect to the location in the various lobes, we were reluctant to accept a statement respecting the particular lobe involved. Very frequently a lesion will appear to be in the upper lobe when it actually involves the upper portion of the right middle or

TABLE III

Number of Pulmonary Cavities Stated to Be Present

Classification	No.	%
Single	241	(90)
Multiple (two, 9; three, 1; four, 1; "several," 6)	17	(6)
Multilocular	11	(4)
	269	(100)

TABLE IV

Location of the Coccidioidal Pulmonary Cavities

Left upper chest (16 "apical")	71
Left lower chest	19
Left chest (location not specified)	7
Total left chest	97
Right upper chest (12 "apical")	77
Right lower chest	45
Right chest (location not specified)	6
Total right chest	128
Total, left and right *upper* chest	148 (70%)
Total, left and right *lower* chest	64 (30%)

of a lower lobe. By tabulations on the basis of "upper" or "lower" chest we observed that 70 per cent were "upper" and 30 per cent "lower." One-eighth were actually reported as "apical," posing emphatically the question of differentiation from tuberculosis.

The first step in the diagnosis of coccidioidal infection is the application of a coccidioidin skin test. This material is the filtrate of asparagine synthetic broth medium, the preparation and use of which have recently been described quite fully.[38] As we have pointed out, a strong reaction does not activate or disseminate a coccidioidal infection, nor does it complicate diagnosis by stimulating the diagnostic precipitins or complement fixing antibodies. When concentrations greater than 1:100 are used, non-specific cross reactions may be confusing, especially in reactors to histoplasmin. However, it must be admitted that in our group of patients with cavities, excluding those diagnosed on the basis of positive coccidioidin and negative tuberculin, 10 per cent were reported to be negative to 1:100 coccidioidin (table 5). Of those diagnosed by culture, one-sixth did not react to 1:100 coccidioidin. Most of those who did not react to 1:100 dilution were posi-

tive to 1:10 coccidioidin. Sometimes they would be completely negative to 1:100 coccidioidin but show a reaction 7 centimeters in diameter with 1:10 material. Three or 3 per cent of the culture positive diagnostic group were stated to be negative to 1:10 coccidioidin. Two of these patients were tested with autogenous coccidioidins made from their homologous strains. One patient did not react to his own, either, while the other is said to have reacted to his autogenous coccidioidin in 1:100 dilution. One's immediate inclination is to hypothecate an antigenic difference in the strains. Such a

TABLE V

Coccidioidin Sensitivity of Patients with Coccidioidal Pulmonary Cavitation*

Diagnostic Group*	Reaction to Coccidioidin								Total	
	Pos. 1:100 (or more dilute)		Neg. 1:100 Pos. 1:10		Neg. 1:100 (not test 1:10)		Neg. 1:10			
	No.	%	No.	%	No.	%	No.	%	No.	%
Culture Pos.	85	(84)	8	(8)	5	(5)	3	(3)	101	(100)
Serum Pos.	127	(95)	5	(4)	2	(1)	0	(0)	134	(100)
Combined	212	(90)	13	(6)	7	(3)	3	(1)	235	(100)

* Group diagnosed on basis positive coccidioidin and negative tuberculin omitted.

situation has never been observed by us in rather extensive studies we have carried out.[1, 38] We have tried to guard against such a theoretical eventuality by including multiple strains as inoculants for our coccidioidins. Evidence that the "strains" did "cover" the three non-reactors is seen in the fact that the patient who reacted to his autogenous coccidioidin but not to our "stock" nevertheless had clear cut serum complement fixation (1:2 ++++, 1:4 +++, 1:8 ++) against antigens which had been prepared from the same strains as were used in preparing the skin testing coccidioidin. The patient who reacted neither to his own nor to our stock coccidioidin had complete fixation of complement in 1:4 serum dilution. The other patient listed as negative to stock 1:10 showed +++ fixation in 1:2 serum dilution. It is clear that the diagnostic humoral antibodies were "covered" antigenically. Indeed, when we tried the autogenous coccidioidin against the homologous serum, it failed to fix complement as effectively as did our stock complement fixing antigen. The failures of the autogenous antigen in complement fixation reflect the fact that satisfactory complement fixing antigen is not easy to prepare. We suspect that the difficulty with the coccidioidin may be associated with various fractions of the coccidioidin. Especially in patients with coccidioidal cavities, the reaction to coccidioidin may be a faint blush, though with considerable induration which is maximal in 24 hours and gone in 48 hours. We had two other patients with coccidioidal cavities reported as failing to react to 1:10 coccidioidin. When the patients were trans-

ferred to Santa Ana Army Air Base, Captain Charles D. Marple [25] tested them personally and found that the men reacted vigorously at 24 hours, though with this faint, easily missed erythema and induration. Readings of the coccidioidin test should be made at 24 and 48 hours. Induration over 5 mm. should be read as positive at either period. Whether these conditions were met in the three patients recorded as negative to our stock coccidioidin in 1:10 dilution is not known. We have noted marked variation in interpretations of the coccidioidin results. In the excellent detailed medical records accompanying specimens sent us from Fitzsimons General Hospital, sometimes one would note the coccidioidin recorded as positive in several army hospitals and negative in others. Properly used and interpreted, the coccidioidin test is the most important and useful "screen." However, like every biological test, it is not perfect.

Of proved aid in diagnosis of coccidioidal infection are precipitin and complement fixation tests.[36] Both tests are generally negative in mild, "inapparent" coccidioidal infections. The precipitins appear before complement fixing antibodies but if the latter do appear, they generally persist longer. With a few exceptions, precipitins disappear within a month or two after the infection has been acquired. By the time most cavities have been discovered, precipitins have vanished. In the group of 134 patients with coccidioidal pulmonary cavitation diagnosed by serological evidence, eight patients showed only positive precipitins. Their cavities developed during the acute coccidioidal illness or in a pneumonic area which appeared during the illness. Thus precipitins may be of use in clinching the etiology of a cavity which appears as a complication of the acute coccidioidal respiratory illness. Once the initial illness is over, the complement fixation test of the serum provides a very important means of aiding in the diagnosis.

In evaluating the efficacy of serological tests in establishing coccidioidal etiology of pulmonary cavitation, we must be restricted to the group in which the fungus was recovered. It should be noted that this restriction selects adversely against the diagnostic significance of the serological tests, for in a considerable number of instances the search for Coccidioides was

TABLE VI

Coccidioidal Complement Fixation in 107 Patients with Pulmonary Cavitation; *Coccidioides immitis* Cultured from Sputum

Complement Fixation	Serum Dilution	No.	%	
Negative (or +)	1:2	28	(26)	(38)
Equivocal (6++; 7+++)	1:2	13	(12)	
Complete (++++)	1:2	31	(29)	
Complete (++++)	1:4	20	(19)	
Complete (++++)	1:8	8	(7)	(62)
Complete (++++)	1:16	5	(5)	
Complete (++++)	1:32	1	(1)	
Complete (++++)	1:64	1	(1)	
		107	(100)	

made and continued until the fungus was demonstrated because the serological tests could not clinch the diagnosis. As table 6 shows, the sera of approximately three-fifths of the culture positive group fixed complement to a diagnostic titer. One-quarter were entirely negative. These facts emphasize that in a very considerable number of instances the etiology of a suspected coccidioidal cavity can be established only by recovery of the fungus.

The frequency of negative or equivocal complement fixation and the relatively low titer of the complement fixation which does occur are in striking contrast to the high titer of complement fixation observed in disseminated coccidioidal infection (coccidioidal granuloma). In table 7 is

TABLE VII

Coccidioidal Complement Fixation Titer in 192 Coccidioidal Pulmonary Cavity Patients with Positive Serology

Highest Serum Dilution Showing Complete Fixation	No.	%
1:2	101	(53)
1:4	58	(30)
1:8	21	(11)
1:16	10	(5)
1:32	1	(½)
1:64	1	(½)
	192	(100)

presented the range in titers of 192 patients with coccidioidal cavitation whose serum fixed complement to a diagnostic titer. Half had complete fixation only in 1:2 serum dilution and 94 per cent went only through 1:8 serum dilution. We have not analyzed all of our complement fixation results in coccidioidal granuloma patients, but seven-eighths certainly fix complement to a higher serum dilution than 1:16. Only two in the cavity group ran up to this usual "range of dissemination."

Observation of serology as cavities developed also elicited evidence against cavity formation implying actual progression of the infective process. We have alluded to the fact that in eight instances, only precipitins were demonstrable before or during the process of cavitation. Among those whose serum fixed complement, three showed no significant change and five showed actual regression by at least one serial dilution as the cavities formed. The presence or absence of the mechanical defect appeared to have no significant influence on the titer of the complement fixation. In three instances we observed the same titer prior to and during cavitation and also after the cavity had closed.

The sedimentation rates seen in table 8 provide further evidence that the infection is usually not active in patients with coccidioidal pulmonary cavities. In nearly three-quarters the rates were normal. Even as cavities were developing, the sedimentation rate would usually return to normal. A few rates continued to be elevated but this is also observed in convalescence

TABLE VIII

Frequency of Accelerated Sedimentation Rates in 149 Patients with Coccidioidal Pulmonary Cavitation by Diagnostic Group

Diagnostic Group	Sedimentation Rate				Total	
	Increased		Normal			
	No.	(%)	No.	(%)	No.	(%)
Culture positive	17	(30)	39	(70)	56	(100)
Serum positive	20	(28)	51	(72)	71	(100)
Coccidioidin pos. Tuberculin neg.	4	(18)	18	(82)	22	(100)
ALL	41	(28)	108	(72)	149	(100)

without cavitation. In contrast, patients with active coccidioidal infections, during either the initial respiratory illness or progressive coccidioidal granuloma nearly always have very accelerated sedimentation rates. While normal sedimentation rates may sometimes be seen in tuberculous cavitation, persistently normal rates are more frequently observed in coccidioidal cavitation.

An understanding of the pathogenesis of these cavities is necessary in deciding on treatment. That these cavities are very likely to remain open is well known. Jamison [18] noted that 19 of his 35 coccidioidal cavities were still open after an average follow-up period of 7½ months. In our series cavities were known to have been present and still open after at least six months of observation in 82 cases. Seventy-two were open over one year, 37 over two years, 25 over three years, 14 over four years and 3 over ten years. From the histories of hemoptysis it is certain that cavities had persisted much longer, but these figures are for actual years of observation of the cavities. In our series only 31, less than half as many of the cavities were reported to have closed, 12 within six months' time and 22 within one year. Three were reported to have closed in the second year of observation, a like number in the third year and one each in the fourth and fifth year. Probably unbeknownst to us many others closed, for usually our facilities were used only for diagnosis and our attempts at follow up of patients from the military-veteran group have not been very successful.

In most instances coccidioidal cavities do not menace the health of the patient. Often he can lead an entirely normal life even if it stays open. We once feared late disseminations and suspected that these patients might develop meningitis or other disasters. However, our experience with lobectomy [27] convinced us that endogenous as well as exogenous reinfection is extremely unlikely. As we noted, this patient's operation was in 1940 prior to the era of chemotherapy. Postoperative empyema resulted in a bronchopleural fistula and extensive sinus formation. Despite the fact that along with pyogenic bacteria the fungus drained from her chest for nearly

four years, she had no metastatic lesions nor extension either to the opposite lung or to the lower lobe of the affected side. Her sinus closed after thoracoplasty and she has been entirely well for four years. The excellent results now being reported in lung surgery for coccidioidal cavitation are further proof that spread from the lesion would be very exceptional, since postoperative extension or spread has never been reported. Thus, unless there is definite indication such as repeated hemoptysis or the troublesome coughing or chest pain which occasionally ensues, the patient may well be left alone to live with his cavity. Unfortunately, a mistaken analogy with tuberculosis is apt to drive us into taking drastic steps which the health of the patient does not warrant.

The possibility of contagion is another reason why vigorous efforts to close a cavity might be undertaken. This point has been discussed previously.[27, 41] There has been general agreement that *Coccidioides* in the sputum does not pose a public health problem. Epidemiological evidence has emphasized the infectiveness of the tiny chlamydospores and arthrospores of dry mycelia. Large numbers of known laboratory infections, infections recognized as having been acquired merely by driving or riding on trains through endemic areas, infections acquired merely by contact with dusty products or clothing—these are eloquent proof of this high infectivity. By contrast, the spherules (sporangia) seen in animal tissues seem poorly adapted to contagion. Rosenthal and Routien [32, 33] recently raised the specter of contagion. In their experiments to demonstrate contagion they exposed tracheas of guinea pigs and then injected spherule-containing pus or sputum into the tracheas and down into the lungs. Naturally enough, lesions developed in the lungs, but a clinical analogy seems remote. There is not space in this paper to discuss adequately the subject of contagion.

It should be stated, however, that in two patients at Fitzsimons General Hospital [24] and one at Baxter General Hospital,[43] coccidioidal cavities removed surgically were observed to contain *Coccidioides* in mycelial form. Thus chlamydospores from dried sputum might float to others just as limited development of mycelia could occur if sporangia-containing pus or sputum was deposited in a moist dark corner. However, all evidence indicates that ordinary hygienic precautions suffice to prevent "contagion." Contrasting with recognition of *laboratory* infections in seven Army hospitals with which we collaborated, no "contact" infection in a ward attendant, nurse or physician has ever been made known to us. Also, though these numbers are small, we have accumulated some "negative" evidence. Our patient previously mentioned convalesced from her lobectomy and spent most of her summers with her parents-in-law. She lived in the San Joaquin Valley. They resided on the coast near San Francisco. We calculated that she lived in their house for a total of five *proved* sputum-positive years and one and one-half years when she also had dressings soaked with pus proved to contain *Coccidioides*. However, both of her parents-in-law failed to react to 1:10 coccidioidin. The veteran whose multilocular cavity is seen in

figure 4, had abundant *Coccidioides* in his sputum up to the time that Dr. Alfred Goldman removed his affected right upper and middle lobes. At the time of the operation his son was six months old. Dr. Robert S. Cleland obligingly coccidioidin tested the baby two months after the surgery and the baby failed to react to 1 : 100 coccidioidin.[5] A First Sergeant in Letterman General Hospital with a pulmonary cavity had sputum and gastric contents consistently positive for *Coccidioides*. Captain T. G. Kabza[20] kindly tested the wife and 18 months old son with 1 : 100 coccidioidin without eliciting any response. We have tested the wife of another veteran with a persisting cavity from which *Coccidioides* was recovered at one time. She did not react even to 1 : 10 coccidioidin, but at the time of her test *Coccidioides* could not be recovered from his sputum, the cavity appearing to be blocked. None of these patients had attempted "isolation" measures, though they were intelligent and presumably had observed conventions of ordinary decency. While five, possibly six, proved exposures of susceptibles is small and criticism may be made that even tuberculosis does not infect at once, it seems fair to conclude that contagion from coccidioidal cavities certainly is not rampant. No one seriously proposes barring travel through coccidioidal endemic areas though resultant infections are proved. Thus the case for preventing exotic coccidioidomycosis by such a "travel quarantine" would seem more plausible than by imposing isolation procedures on patients. A corollary is that closure of a coccidioidal cavity does not seem imperative on the grounds of public health which apply to "sputum positive" tuberculous cavities.

We formerly shared with Winn[42] some enthusiasm for pneumothorax treatment. In six of our group closure of a cavity was reported following institution of pneumothorax. Willett and Weiss[40] reported the closure of one cavity after a pleural effusion and we noted two others. In one additional patient effusion occurred as a complication of pneumothorax treatment and the cavity remained closed after the fluid absorbed. While pneumothorax treatment apparently has aided some patients, in 10 of our group the treatment is known to have failed. Either the cavity was not closed or if it did close it reopened. This reappearance of a once-closed cavity is most discouraging. An explanation of why some cavities do not remain closed may be the several reports we have received of epithelialization of cavity linings. A contraindication to pneumothorax is a subpleural cavity. Collapsing the lung brings the very real danger of bronchopleural fistula and spontaneous hydropneumothorax.

Treatment by phrenic crush as advocated by Denenholz and Cheney[7] is credited with closing at least four of the cavities of this group. Incidentally, the closure of the three and four year old cavities mentioned previously occurred after phrenic interruption. With his very considerable experience in this field, Willett is optimistic about this treatment. Obviously, it is not a sure cure. In our group a half-dozen were not benefited by its use. However, its benign nature recommends it for appropriate cases.

It would appear that if cavitation develops during the initial infection, strict bed rest should be continued even after temperature and sedimentation rate seem normal. However, with old cavities it must be admitted that bed rest alone has rarely proved useful, as Jamison's experience also indicates. Denenholz and Cheney [7] combined it with shot bag immobilization, though this, too, has limited use. Our own faith in the value of rest was badly shaken by an experience at Minter Field. Convalescing from a coccidioidal pneumonitis he developed in May, one of the enlisted men in the Medical Detachment developed a cavity in the area of consolidation. He was kept in bed several months and then cautiously allowed up. His cavity gradually closing, he was discharged from the hospital, but was excused from physical training and restricted in his duties. We congratulated ourselves on how splendidly we were managing him until we discovered his cavity closure had been completed while he was the star end of the Minter Field football team.

When coccidioidal cavities evoke symptoms but fail to close on a trial of rest or phrenic crush, lung surgery may be undertaken without misgiving. Our former emphatic stand against such radical treatment resulted from the complications in our patient following lobectomy.[27] However, her difficulties would not have arisen had antibiotics been available in 1940. Lobectomies and resections have succeeded in a score of patients with coccidioidal cavities. Recently Rogers [30] merely shelled out a thin-walled coccidioidal cavity and approximated the lung tissue. Controlling bacteria with antibiotics results in uncomplicated healing. An operation does not stir up infection even to the extent of increasing the titer of complement fixation. In four patients postoperative serological titers continued negative. One had a postoperative pneumonia, but the absence of complement fixation indicated that *Coccidioides* was not responsible. Of four instances in which serum fixed complement prior to lobectomy, the titers fell one serial dilution immediately after operation. However, they continued at that reduced level. It would appear that part but by no means all of the infected tissue had been removed. Roger's patient from whom the cavity merely had been excised showed no change in low but conclusive (++++ in 1:2) complement fixation. Thus surgery can be performed for coccidioidal cavitation without dissemination and even without local spread as long as bacterial infection is kept under control. Apparently *Coccidioides* poses no special risk. Except in the immunologically defective "disseminators," coccidioidal immunity is surprisingly solid. Since we consider any thoracotomy is serious, we do not advise lung surgery unless a cavity really causes disability. Furthermore, a word of caution is advisable. While immediate results of this lung surgery have been excellent, follow up to eliminate possibility of unforeseen complications is imperative.

However, even though "silent," peripheral (subpleural) persistent coccidioidal cavities may well warrant "prophylactic" lung surgery. Regardless of how one regards pneumothorax treatment of coccidioidal cavities in

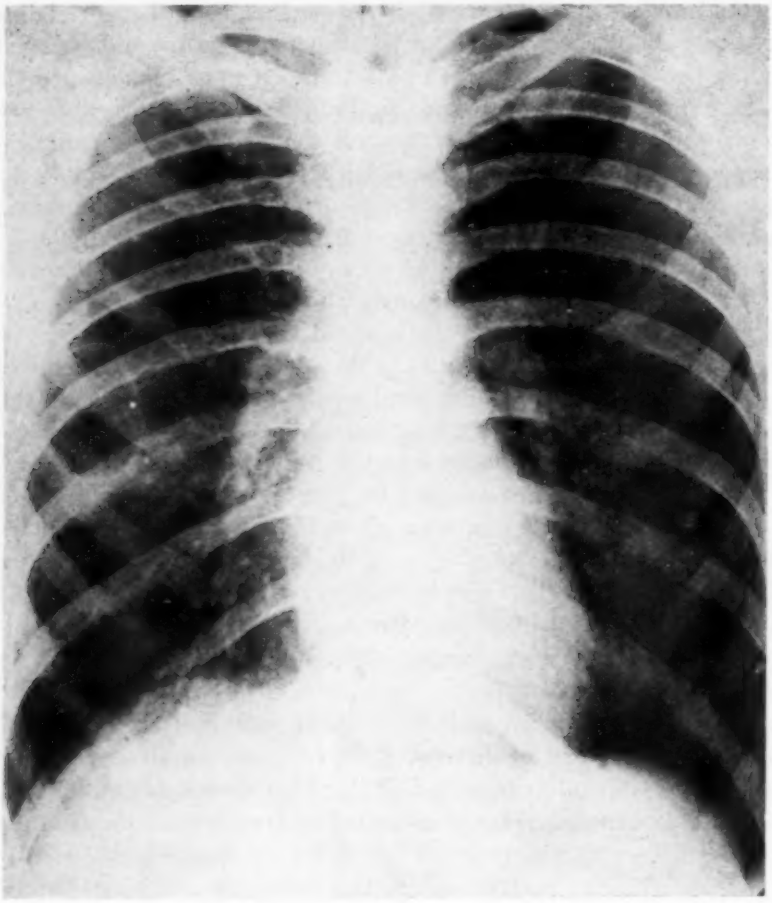

FIG. 5A.

other locations, it is contraindicated in such patients. A subpleural cavity presents the risk of tearing into the pleural space and causing spontaneous hydropneumothorax. The following illustrative case typifies this problem. A detailed history was sent us by Captain T. E. Finegan [12] who was associated with Captains R. Sleeter and C. S. McGill in the care of the patient at Madigan General Hospital.

A 26 year old white male lived in Pixley, California, in the heart of the coccidioidal endemic area of the San Joaquin Valley from 1935–1942. He joined the Navy in 1942 and returned home from time to time. Because of cough, hemoptysis and considerable sputum while on sea duty in 1945, he was returned to the United States. In September 1945 he entered Corona Naval Hospital with the diagnosis of tuberculosis, pulmonary, reinfection, active, moderately advanced. He had a 2.4 cm. thin walled cavity in the periphery of his right lung at the level of his seventh dorsal vertebra. His sputum and gastric specimens were negative for *M. tuberculosis* and his sedimentation rate was only 10 mm. A serum specimen was sent us in No-

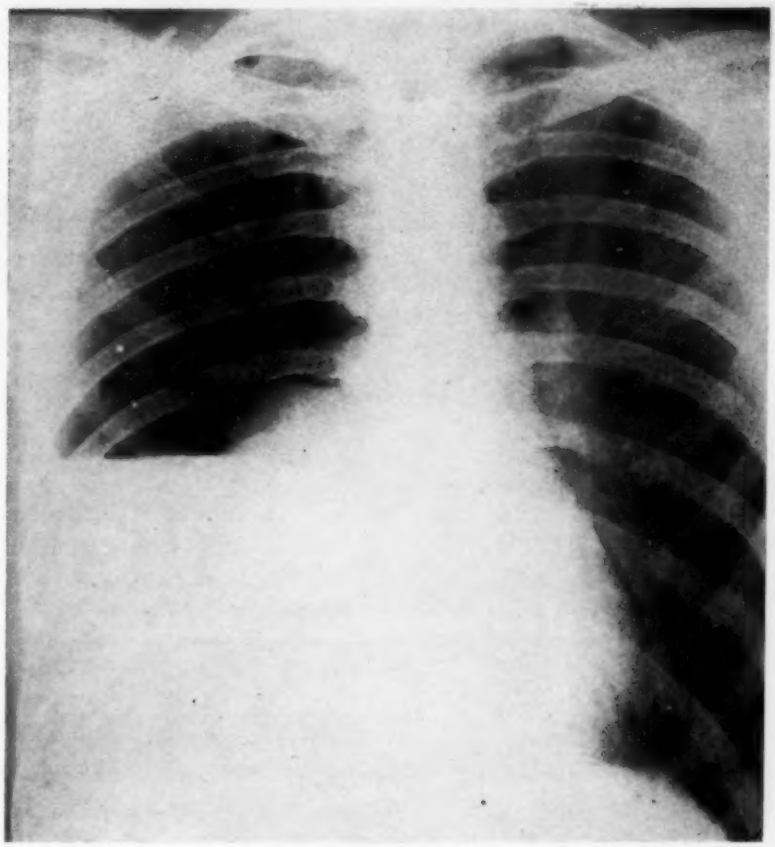

FIG. 5B.

vember and revealed complete fixation of complement through 1:4 dilution. His 1:100 coccidioidin was negative, as was his 1:1,000 tuberculin. We have no record of a 1:10 coccidioidin. He was discharged to the Veterans Administration and left the Los Angeles Veterans Administration Hospital in March 1946 with cavity still present after over six months of continuous hospitalization. In October 1946 he moved to the state of Washington. We received another serum specimen from him then which was identical with the initial one a year previous. He managed fairly well but tired easily. When fatigued, he coughed and raised considerable sputum which was frequently bloody.

On June 6, 1947, he developed a high fever, malaise and severe cough. He was treated by a private physician with penicillin and sulfonamides. His temperature dropped, but was still 101° F. in the afternoon for some time. The roentgenogram taken June 20, 1947 (figure 5A), shows the large thin walled peripheral cavity. On June 27, 1947, he was awakened by a very severe pain in his right chest followed by shortness of breath. He entered Madigan General Hospital the next day. A roentgenogram (figure 5B) confirmed the physical examination which revealed hydropneumothorax with fluid to the level of the sixth rib anteriorly. He was treated with bed rest and repeated thoracenteses with additional removal of air. As the series in figure 5 shows, the fluid level fell and the lung reëxpanded, although not completely. As late as January 15, 1948, 500 c.c. of fluid were removed. The old

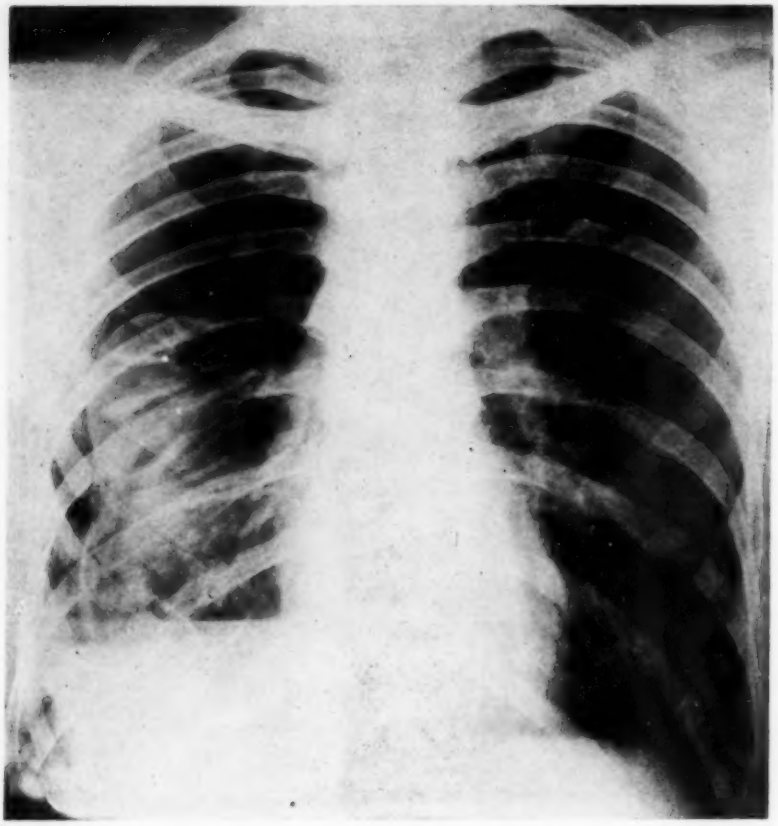

FIG. 5C.

cavity could not be seen. The patient felt quite well. A fungus recovered from the fluid by Lt. M. S. Heep was confirmed by us as *Coccidioides immitis*.

Seven or 2.6 per cent of the entire group of coccidioidal cavity patients developed spontaneous hydropneumothorax. As a complication of pneumothorax treatment, a bronchopleural fistula and pyopneumothorax occurred in an eighth. This patient had a pneumothorax for a "tuberculous" cavity but no tubercle bacilli had ever been demonstrated and Coccidioides was recovered from his empyema and sputum. We performed confirmatory studies on four other patients with spontaneous hydropneumothorax but whether there was antecedent cavitation is not known. Their histories indicated they were not undergoing primary coccidioidal infections at the time of the onsets of pneumothorax. However, during the course of clear-cut primary coccidioidal infections, spontaneous hydropneumothorax developed in three persons. One is included in the seven patients with known antecedent cavities. In the other two no cavity had been demonstrated. We saw another patient with repeated episodes of spontaneous pneumothorax shortly after his coccidioidal infection was acquired. They were incomplete

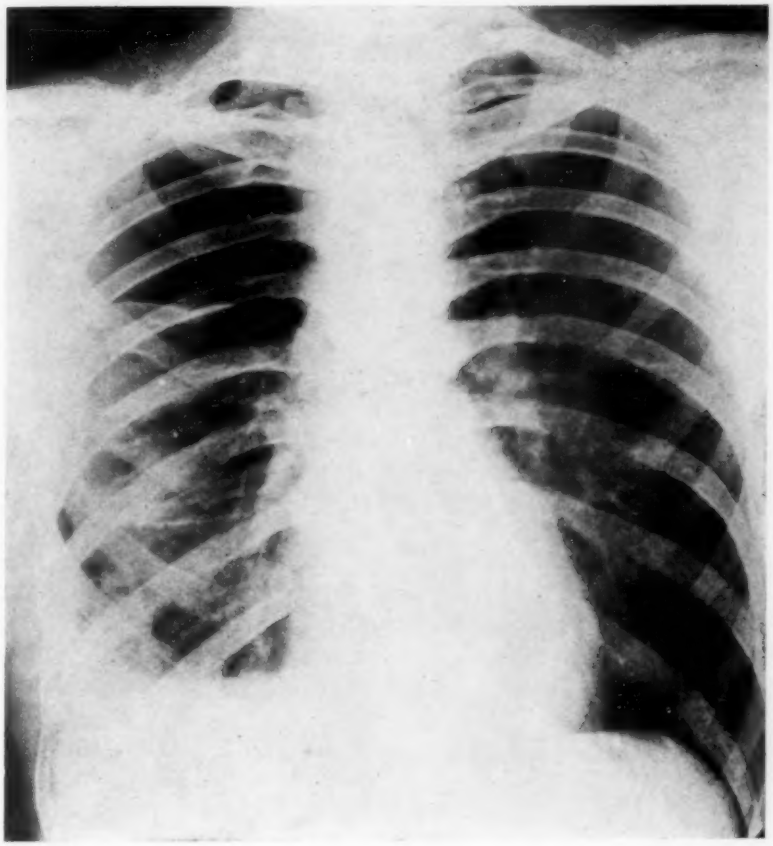

FIG. 5D.

and no fluid formed. However, this experience indicates that spontaneous hydropneumothorax can occur during initial infection without definite cavity formation. In one civilian and one soldier who underwent spontaneous hydropneumothorax during these acute initial infections, severe diabetes mellitus developed. Previous examinations of the soldier's urine established the association of the diabetes with the infection. The civilian had been circumcised under a general anesthetic only a month before and his preoperative urine examination revealed no sugar.

From the fluid of each of the 14 patients with coccidioidal hydro- or pyopneumothorax the fungus was recovered. In one [29] tubercle bacilli were also recovered. Thoracotomies with excision of the fistula and decortication were performed in four. Three of the four regained full lung expansion but in the fourth subsequent thoracoplasty was necessary to obliterate pleural space. The patient with post-pneumothorax empyema required intercostal skin-flap drainage and thoracoplasty. As in simple lobectomies and cavity resections, this more drastic surgery never resulted in disseminations or other coccidioidal complications.

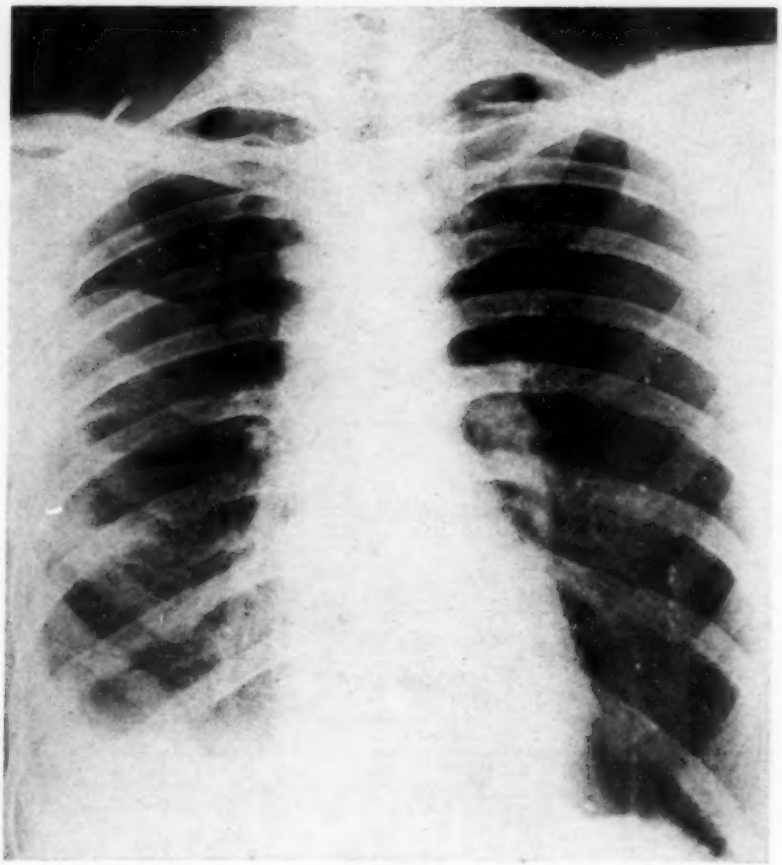

FIG. 5E.

FIG. 5. Development of spontaneous hydropneumothorax as complication of peripherally located coccidioidal cavity. The series of roentgenograms was reproduced by Madigan General Hospital Photographic Laboratory and made available from files of the Army Medical Museum. For account of case see text.

A. Pre-admission roentgenogram seven days before spontaneous hydropneumothorax. Peripheral thin-walled cavity in right lung.

B. Admission roentgenogram two days after spontaneous hydropneumothorax showing collapsed lung, fluid and mediastinal shift.

C. Some expansion of lung and less fluid two months after spontaneous hydropneumothorax.

D. Progressive improvement three months after hydropneumothorax.

E. Continued reëxpansion and small amount of fluid four months after hydropneumothorax.

However, seven months after spontaneous hydropneumothorax, lung was incompletely expanded and some fluid was present.

SUMMARY AND CONCLUSIONS

Coccidioidal pulmonary cavitation may develop in an area of pneumonitis or in a residual lesion some months after the primary infection. Patients with cavities rarely disseminate their infections, appearing to possess an

effective immunity mechanism. Frequency of cavitation in inapparent coccidioidomycosis is not known. The cavitation incidence in Army hospitalized cases of coccidioidomycosis has ranged from 2 to 8 per cent.

Coccidioidal etiology of 274 pulmonary cavities was verified by recovery of the fungus in 40 per cent, positive serology in 49 per cent and positive coccidioidin and negative tuberculin in 11 per cent. Double infections, tuberculous and coccidioidal, were seen in seven of the group. In none was the coccidioidal infection progressive and in only one was tuberculosis progressive.

The relatively benign nature of these cavities is indicated by the fact that in the military patients three-fifths of the cavities were incidental discoveries and only two-fifths of the diagnoses resulted from symptoms. Among civilians nearly three-fifths of the initial roentgenograms were taken because of hemoptysis which, however, was rarely a real menace to health. The other signs and symptoms of tuberculosis were strikingly infrequent.

Ninety per cent of the cavities were single and 70 per cent were located in the upper chest.

A coccidioidin skin test is the first diagnostic step. Approximately 10 per cent may require coccidioidin stronger than 1:100. A few may be negative even to 1:10, but, misunderstanding in the interpretation of the skin tests frequently accounts for reported negatives. If antigenic strain variations occur, they are exceedingly infrequent.

Where serology is negative and the tuberculin test is positive, the diagnosis can be established only by recovering the fungus from sputum or gastric contents. In three-fifths of the sputum-positive patients with coccidioidal cavities proof of etiology could also be established serologically. When positive, fixation of complement was usually only to a low titer in distinction to the high titer characteristic of disseminated infection. Even while cavities were forming, decline in titer of complement fixation and slowing of sedimentation rates were noted. Three-quarters of the sedimentation rates reported to us were normal.

In treating cavities, one must realize that while many cavities close quickly, a considerable proportion may remain open for many years, rarely producing serious health problems. Bed rest doubtless aids in closing cavities early in their evolution, but has limited value later. The risk of dissemination being negligible and possibility of contagion very remote, drastic intervention should be reserved for specific indications. Phrenic interruption sometimes succeeds in closing even long established cavities. Pneumothorax may be used in selected cases but not with peripheral cavities because of the hazard of creating a bronchopleural fistula. Qualified thoracic surgeons have successfully performed many lobectomies, wedge resections and at least one simple excision of coccidioidal cavities. The high level of immunity in patients with cavities eliminates hazard of dissemination or even local extensions as long as bacterial infection is prevented.

Surgical removal of a persistent subpleural cavity may be undertaken to eliminate the hazard of spontaneous hydropneumothorax. Of 13 patients with coccidioidal spontaneous hydropneumothorax, seven were demonstrated to have had antecedent cavities. Thus spontaneous hydropneumothorax occurred in 2.6 per cent of our patients with coccidioidal cavities. Four were treated successfully by excision of the bronchopleural fistula and decortication. One other patient with cavity developed pyopneumothorax as a complication of pneumothorax treatment. Success of appropriate lung surgery and freedom from dissemination and local spread again were notable in these five surgically treated cases.

Coccidioidal cavitation and spontaneous hydropneumothorax, while admittedly undesirable, are much less hazardous than similar appearing tuberculous lesions and incomparably less dangerous than the disseminating coccidioidal granuloma.

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THE TREATMENT OF ROCKY MOUNTAIN SPOTTED FEVER WITH CHLOROMYCETIN *

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THE demonstrated efficacy of Chloromycetin in the treatment of human cases of scrub typhus [1] encouraged belief that this new antibiotic might likewise prove effective in the therapy of Rocky Mountain Spotted Fever. During the months of May, June, and July, 1948, a total of 17 cases with the clinical diagnosis of Rocky Mountain Spotted Fever were treated with Chloromycetin.† In 16 of these cases adequate confirmation of the clinical diagnosis was obtained through animal inoculation and serological tests. One of these cases was discarded because of the stage of the disease. The present report deals with the therapeutic results obtained in the remaining 15 proved cases.

Chloromycetin was originally prepared by Ehrlich and associates [2] from liquid cultures of a Streptomyces originally isolated by Burkholder ‡ and shown by him to possess antibacterial activity. It is a crystalline substance relatively insoluble in water, but well absorbed from the gastrointestinal tract. In spite of its bitter taste it is well tolerated when given orally and serum levels of the drug after oral administration have been found to be parallel with those after parenteral injection. The toxicity of the drug is apparently low. When given intravenously in mice and intramuscularly in dogs,[3] Chloromycetin is well tolerated in single doses up to 100 mg./kilo body weight. Dogs injected intramuscularly twice daily with 36 to 44 mg./kilo of Chloromycetin for 24 days developed a moderately severe anemia, without significant changes in the white blood cells and without disturbance in hepatic or renal function. Since the Chloromycetin was in colloidal solution in 62 per cent propyleneglycol, it is not clear that the anemia can be attributed solely to the antibiotic.

Reports up to the present time on the therapeutic use of Chloromycetin orally in man have indicated the absence of any toxic manifestations. These reports, however, have dealt solely with Chloromycetin used over short periods up to 8 to 10 days. Whether the continued use of the drug in

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† The Chloromycetin used in this work was furnished by the Research Division of Parke Davis and Company.

‡ Dr. Paul R. Burkholder, Osborn Botanical Laboratory, Yale University.

humans for long periods of time would provoke toxic symptoms is as yet unknown.

The initial studies of the antibiotic spectrum of Chloromycetin in vitro and in vivo in animals indicated outstanding effectiveness in rickettsial infections of chick embryos and mice.[3, 4] In human rickettsial infections Chloromycetin has demonstrated curative properties in scrub typhus fever [1] and in epidemic typhus.[5, 6] It has also been shown to exert a specific therapeutic effect in typhoid fever.[7]

Selection of Cases. The Eastern form of Rocky Mountain Spotted Fever is endemic in Maryland. The common proved vector of the disease is the dog-tick, *Dermacentor variabilis.* The seasonal incidence of the disease begins usually in May, reaching its peak towards the end of June and falling rapidly in the later summer months. The annual total number of reported cases in this state has averaged 57.6 in the last 10 years. The majority of the cases occur in the Eastern half of the state.

Coöperation of practicing physicians in the affected counties resulted in the reference of a considerable proportion of the cases of Rocky Mountain Spotted Fever occurring during the period of this study, to the University Hospital in Baltimore. During this time 19 cases were so referred with the clinical diagnosis of Rocky Mountain Spotted Fever. Of these, two were not treated with Chloromycetin.* In the remaining 17 cases the clinical diagnosis of the referring physician was concurred in and treatment instituted.

In one of these 17 cases laboratory confirmation of the diagnosis was not obtained. In this case the clinical response to the drug was prompt and favorable, but for the purpose of this report the case is excluded from consideration. In a second case, admitted on the twenty-first day of the disease, treatment was not begun until the twenty-second day and though this case was proved by positive agglutination and complement-fixation tests and showed characteristic drop in fever to normal during therapy with Chloromycetin, it has been excluded from the report because of the uncertainty at this late stage, as to whether the fall in fever should be attributed to the effect of the drug or to spontaneous abatement of the disease. There remained therefore the 15 cases, here reported, in which the clinical diagnosis of Rocky Mountain Spotted Fever was made and confirmed by later laboratory findings and which were treated with Chloromycetin and observed throughout the remainder of their febrile course and convalescence in the hospital. Ten of these patients were under 16 years of age (2 to 16) and five above this age (17 to 64). Seven were males and eight females. All were white.

* In one case, a female child of 5, the clinical diagnosis was considered doubtful and there was an accompanying acute appendicitis with a leukocytosis of 20,000. The second case, an infant of 4, was brought into the Accident Room in extremis and died there in three hours.

Diagnostic Criteria. A. Clinical. In the establishment of the clinical diagnosis the following factors in the history and examination were considered of primary importance:

a. History of exposure to ticks and of tick bite. All 15 cases gave a history of exposure to ticks and 12 a history of the removal of an attached tick within the two weeks preceding the onset of their febrile disease.

b. Persistent fever since the day of onset. In all cases the history indicated that fever had been present daily from the date of onset until admission. In 11 cases the patient was observed in the hospital over a period of from 24 to 72 hours prior to administration of specific therapy and the presence of continued fever confirmed. In four cases the severity of the patients' illness precluded this period of observation.

c. Characteristic rash. In all cases a rash, characteristic both as to individual lesions and as to distribution, was observed prior to the initiation of specific therapy. In a number of cases the rash was considered only suggestive on admission but became fully characteristic during the period of observation prior to therapy.

d. Secondary clinical features. When present the following symptoms and signs were considered to favor the diagnosis of Rocky Mountain Spotted Fever: prominence of headache, mental dullness, torpor or delirium, palpable spleen (especially in children), tarsal conjunctivitis, slight periorbital edema and photophobia.

e. Absence of evidence by history, physical examination and laboratory tests of other infectious disease. No evidence of another type of infection capable of producing the clinical picture was found in any case. Blood cultures were made in each case and were uniformly negative.

*B. Laboratory.** Confirmation of the clinical diagnosis of Rocky Mountain Spotted Fever was sought in each instance through the following procedures:

a. Blood was drawn prior to the initiation of Chloromycetin therapy and, an average, of four times during therapy. From each blood sample two male guinea pigs of approximately 250 grams were injected intraperitoneally with 4 c.c. of suspended blood cells. The initial blood sample of 8 to 10 c.c was allowed to clot in an incubator, the serum decanted, the remaining clot ground up in 8 to 10 c.c. of saline solution and the total then divided into two portions for injection. Temperatures of all guinea pigs were taken daily for 21 days. A rise of temperature above 104° F. over three consecutive days or more was considered positive indication of transmission, if later confirmed by complement-fixation in the guinea pigs' serum. In the present study a positive complement-fixation was obtained from the blood of all pigs showing a positive febrile response.

* Grateful acknowledgment is made to the following laboratories which performed the serological tests: Department of Clinical Pathology, University Hospital, Baltimore, Md.; The Department of Virus and Rickettsial Diseases, Army Medical Center, Washington, D. C.; Maryland State Department of Health.

b. Agglutination tests for Proteus OX19 were performed in all cases prior to the administration of Chloromycetin and thereafter approximately every four days while in the hospital. In some instances blood was obtained at irregular intervals after discharge of the patient. Agglutination titers higher than 1 : 160 were considered positive.

c. Complement-fixation tests. Each patient's blood was tested for complement-fixation against the antigen of *Rickettsia* (*Dermacentroxenus*) *rickettsi* prior to therapy and whenever blood was drawn for agglutination test thereafter. Complement-fixation with titers of 1 : 10 or higher were accepted as positive.

In evaluating results of laboratory diagnostic procedures in individual cases, a strongly positive reaction in any one of the three categories, that is animal inoculation, agglutination of OX19, or complement-fixation, was accepted as adequate confirmation of the clinical diagnosis.

In the 15 cases which constitute this series, six gave positive results by all three methods, eight gave positive reactions by two tests and one by one test only. There were seven cases in which guinea pig inoculation proved positive; 14 cases gave positive agglutination tests; and 15 positive complement-fixation reactions.

Specific Therapy with Chloromycetin

a. Method of administration. Chloromycetin, furnished by the research division of Parke Davis and Company for the purposes of this experimental study, was in the form of 0.25 gm. tablets. These were administered orally. In adults and in many children whole tablets were swallowed. In general in spite of the bitter taste of the drug, surprisingly little difficulty was experienced with oral administration. In some young children the tablets were pulverized and suspended in water or in dilute chocolate syrup, or given in gelatin capsules. In one instance it was necessary to administer the drug by gavage. Vomiting of the drug on initial administration occurred in two or three cases, but was satisfactorily handled by one or another of the methods mentioned above.

b. Dosage. The dosage regime adopted was empirical, being based in general, however, on doses reported as effective in scrub-typhus fever. Following a large initial dose the drug was given on a three hour schedule. In the first four cases therapy was continued for four days after the temperature reached permanent normal levels. In the remaining cases the policy was adopted of discontinuing the drug when the temperature had remained below 100° F. (rectally) for 24 hours.

The initial dosage was 50 mg./kilo in cases 1 and 2 of the series. Thereafter it was raised to approximately 75 mg./kilo of estimated weight. In case 11 in which gavage had to be employed, an initial dose of 128 mg./kilo was administered. The initial dose was usually administered in two or three parts at approximately one hour intervals.

After the initial dosage the drug was given at three hour intervals day and night. Arbitrary dosages employed were 0.25 gm. every three hours for children under 16 years of age (10 cases), and 0.5 gm. for those above this age.

Therapeutic Effects of Chloromycetin Treatment

a. Clinical status. Improvement in patients' symptoms was uniformly observable but not striking in the first 24 hours. However, on the second day of treatment abatement of such symptoms as headache, mental dullness, etc., was definite. The eruption did not spread following initiation of treatment and by the end of the second day had markedly receded. On the third day, in the majority of cases, the patient was plainly convalescent with interest in his surroundings, increased strength, return of appetite and freedom from symptoms.

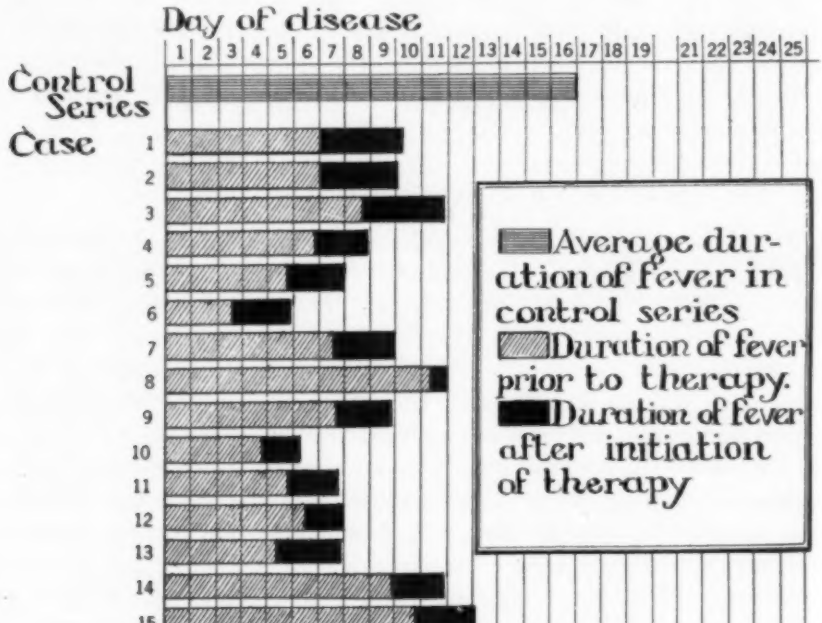

Fig. 1. Duration of fever in 15 cases of Rocky Mountain Spotted Fever treated with Chloromycetin contrasted with average duration of fever in a control series of 46 cases.

b. Fever. The recorded data as to the effect on the febrile course constitute the most striking evidence of the therapeutic effectiveness of Chloromycetin in this disease. Irrespective of the height of the preceding fever or the age of the patient, Chloromycetin therapy was followed in all cases by fall of temperature to normal levels within 76 hours (figure 1) after the initial dose. The average duration of fever after initiation of therapy was considerably less, approximately 2.2 days.

Temperatures were taken rectally at four hour intervals day and night in these patients. Normal temperature level was defined as rectal temperature remaining under 100° F.

In no instance after normal temperature had been reached and remained normal for 24 hours was there any secondary rise which might be interpreted as a relapse; nor did fever appear during convalescence, suggestive of a recurrence of the disease.

c. Rickettsiemia. In the seven cases in which the guinea pig inoculations from blood taken prior to the initiation of therapy proved positive, inoculation of further guinea pigs with the same patient's blood taken after the initiation of therapy, yielded no febrile response in the guinea pigs. In each of the seven cases blood was drawn two to four times on successive days beginning with the second day of treatment and two guinea pigs inoculated on each occasion. A total of 34 guinea pigs were thus utilized.

These negative findings suggest that rickettsiemia disappears rapidly after the initiation of Chloromycetin therapy. However, the possibility is not covered that some of these pigs might have acquired an inapparent infection which would be detected only by complement-fixation tests on their blood. Further work and a larger series will be required to settle this point.

d. Development of immune bodies. Increasing titer of agglutinins for Proteus OX19 and of complement-fixing antibodies was observed in these 15 patients during convalescence following Chloromycetin therapy. It would appear that the premature termination of the active disease by Chloromycetin does not alter the usual course of development of these immune bodies.

e. Convalescence. From the clinical point of view convalescence of these cases proceeded in normal fashion. It was proportionate in length to the severity and duration of the initial febrile period of the disease.

Evidences of Toxicity of the Drug. Mention has been made of the fact that on initiation of therapy vomiting of the first or second dose occurred in a few cases. In no instance, however, did vomiting persist. It was our impression that psychic factors as well as the bitter taste were responsible for such vomiting as occurred. No diarrhea or jaundice was observed. Repeated urine examinations showed no evidence of significant albuminuria, casts or crystals. Analysis of the blood counts during and after treatment showed no striking variations from their original levels.

Comparison with Control Series

In order to be able to compare the Chloromycetin treated cases with a series of cases of Rocky Mountain Spotted Fever which did not receive any specific chemotherapeutic agent, an analysis was made of the records of 46 cases of this disease admitted to the University Hospital prior to availability of para-aminobenzoic acid therapy or Chloromycetin. In figure 2 is shown graphically the day of disease on which the febrile course in each of these 46

cases terminated. It is evident that the natural course of the fever in this disease usually terminates between the thirteenth and the twenty-first day of the illness. The average duration of fever in these 46 cases was 16.04 days. These 46 cases comprise the total number of cases, admitted during the period 1930 to 1946, which recovered and which showed no complications that might have prolonged their febrile course.

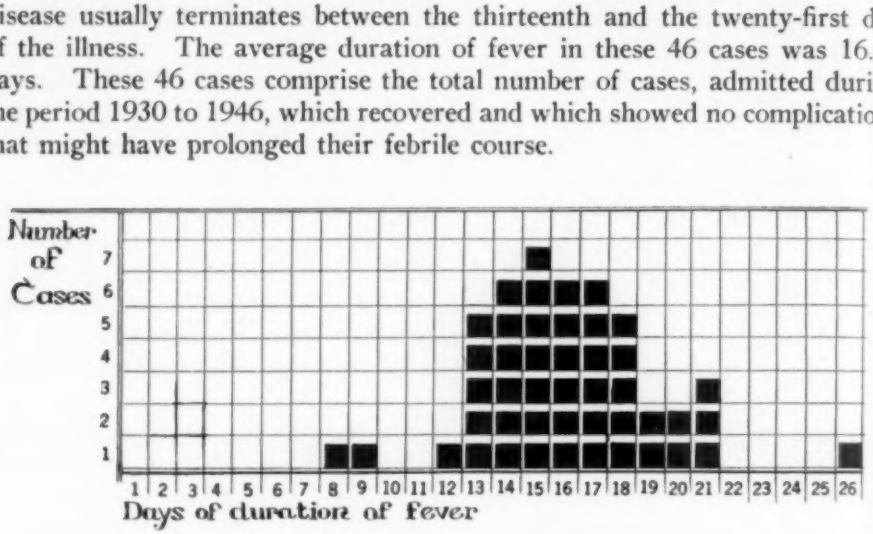

FIG. 2. Duration of fever in 46 non-fatal cases of Rocky Mountain Spotted Fever in Maryland which did not receive specific therapy. Cases with complications which might prolong fever were excluded. Black squares indicate day of disease on which fever terminated.

In contrast figure 1 indicates the day of the disease on which fever terminated in each of the 15 cases treated with Chloromycetin. The uniform shortening of the duration of the febrile course as a result of therapy is plainly evident.

Statistics of the Maryland State Department of Health show that 576 cases of Rocky Mountain Spotted Fever were reported in the years 1938 to 1947 inclusive. The number of deaths for this period was 120, giving a mortality rate of 20.8 per cent. In the Chloromycetin series there was no mortality. Among the 15 cases of this series four were classed clinically as virulent forms of the disease.

DISCUSSION

It is considered that the evidence presented indicates that the new antibiotic Chloromycetin, in addition to its previously demonstrated effectiveness in the treatment in man of scrub typhus and of epidemic typhus is also an equally effective agent in the treatment of Rocky Mountain Spotted Fever. Further studies will be required to determine whether murine typhus, Q fever, and other members of the family of rickettsial diseases will yield in similar fashion to this therapeutic agent.

The question of the proper dosage of the drug and particularly the number of days during which its administration should be continued, is still undetermined. In the present relatively small series of cases no instance of

recurrence of the disease was observed when the drug was discontinued after 24 hours of normal temperature. This schedule was employed for investigative purposes and because of the scant information as yet available bearing on possible toxic effects of long continued administration. A very much larger experience with the use of Chloromycetin in Rocky Mountain Spotted Fever is required to demonstrate whether such a brief course of treatment is adequate to eliminate completely the rickettsial infection. The occurrence in animals of inapparent infections and the suggestive evidence, indicating that Brill's disease in humans is due to the recrudescence of a latent rickettsial infection, both point to the possibility that incomplete therapy might be followed by a latent form of Rocky Mountain Spotted Fever.

Conclusions

The results of treatment of 15 cases of Rocky Mountain Spotted Fever with the antibiotic Chloromycetin indicate that this drug is an effective therapeutic agent in this disease.

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PSYCHOANALYSIS *

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MODERN psychiatry is based on the fundamental contributions of three men. Cannon intensely studied the physiological manifestations and ramifications of emotions. Pavlov conducted ingenious research on the nervous system integrations involved in the process of learning, habit formation, and conditioning. Freud traced the origins of many neurotic illnesses to childhood and infantile experiences and investigated the complex conditionings of the individual in his family life. These conditionings he believed in many instances established the predisposition to neurosis and psychosis.

The family is the primal social relationship. In the interactions of parents and children in the family setting, infants and children experience feelings which are most important in the development of the personality. Feelings and emotions are the heart of the personality. Experiences determine or condition feelings. Persons in the family by their attitudes and behavior induce and establish feelings that are often characteristic of an individual for life, frequently determining his success or failure and his health or morbidity.

Parents or their surrogates in their contacts and handling of even very young children can produce four general groups of feelings. 1. Security and well-being. 2. Insecurity and fear. 3. Irritation, anger, temper. 4. Tension, uncertainty, worry, and depression.

Security and well-being are given by experience of warmth, gentleness, tenderness, support, care, dependability, ministrations to and satisfactions of basic needs, and love. Insecurity and fear are stimulated by delay and deferment of basic gratifications, aloneness, lack of care, deprivation, and rejection. Irritation and anger are aroused by discomfort, impatience, roughness, lack of satisfaction of soothing stimuli, forcing, and frustration. Worry and depression are excited by irregularity, uncertainty, inconsistency, indifference, neglect, and deprecation.

The early expression of tensions, unsatisfied hungers, fear, overstimulation, and anger is in crying. These emotions are, early, not always clearly differentiated, and find common pathways of expression in unorganized hyperactivity of the skeletal musculature and crying. The various bodily systems, such as the respiratory, circulatory, gastrointestinal, and urinary systems, participate vigorously in these reactions. Later the emotions of fear, anger, and depression become differentiated by stimuli, organization, thought content, and type of activity. All of these involve intense physiological disturbances. Crying of course drops out except in unusually intense situa-

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From the Institute of the Pennsylvania Hospital.

tions. But intense physiological disturbances within, remain as the chief outlet or expression of emotions. These physiological disturbances acquire a pattern through repetition that is often characteristic of an individual. The physiological manifestations in characteristic form for a given individual form a sort of body language or organ language. Thus nausea may be the expression of dissatisfaction or disgust; diarrhea of insecurity and worry; colitis and migraine of anger; tachycardia and palpitation of fear; and constipation of restraint, resistance, and stubbornness. This organ or body language constitutes the so-called *organ neuroses* or *neurasthenia.* The intensity and emphasis of the physiological responses make them more apparent and important than their psychological content.

A sort of law might be formulated. Early in life physiology expresses what is later psychology. Later in life psychology (attitudes, thoughts, feelings) often uses early patterns of physiology to express itself.

The successful, mature adult must have the following characteristics. He must be secure, independent, take responsibility, coöperate with others, be able to tackle and to solve problems, and love or be devoted to persons, things, activities, movements, institutions, or causes, beyond himself.

Security and self-confidence are necessary to approach the new, to meet changes, to stand alone. Courage is necessary to tackle uncertainties. Confidence and courage are required to develop independence; to make decisions, become decisive, and self-directing (i.e., not too dependent). The effective adult must be able to take responsibility. He must act on his own initiative, develop plans, and organize his activities. He must carry through, be reliable and accountable. The mature person is able to coöperate with others. He can work, apply his skill, exert effort, and persevere. The successful adult must be able to meet problems, uncertainties, mistakes, frustrations, disappointments, rejections, limitations, deprecation, unfairness and meet them constructively. That is, he must meet such circumstances without developing unusual or handicapping bodily discomforts or intense emotionalism. If these make one unhappy or ineffective, his condition is called a psychoneurosis. If they are so intense that the individual is unable to work or get along with his fellows (with elated, depressed, paranoid, or schizophrenic mechanisms), the state is called psychotic. In both of these states the old incoördinations of childhood (psychoneuroses) or infancy (psychoses) are reawakened and expressed in musculo-skeletal, visceral, and intense emotional reactions. This reawakening or return to former, older patterns of response is called *regression.*

The infant and young child are constituted essentially of physiology, instinctual feelings, and actions. With cortical development, physiological and instinctual-emotional energies become channelized and organized into patterns of effective neuromuscular actions, under the acquisition of skills, socially approved goals, and conditioning or training. Defective, traumatic, unwise conditioning and frequent physical disease interfere with effective organization and development. Severity of these handicaps (too much ex-

perience of lack of well-being, fear, tension, anger, etc., in the early home environment) and chances of development determine whether the individual will develop as: 1. a rugged, normal personality; 2. an apparently normal person with, however, instability and a tendency toward regression; 3. a person with obvious handicaps such as dependency, or lack of initiative and aggression; 4. a person thrown back into regressive physiological reactions such as conversion hysteria, neurasthenia or hypochondriasis; 5. one with intense exaggerated emotion as in anxiety hysteria or obsessional neurosis; 6. or one with completely disorganized patterns such as manic-depression and schizophrenia. Thus an individual becomes a thalamic, emotional, viscerally organized person with the typical expressions, instead of one with a cortico-skeletally patterned organization. The training the child receives, his conditioning, determines whether adult adequacy, defective development, or instability and readiness to regress to thalamic responsiveness, result.

The family is the place where organization and control are developed or susceptibility to disorganization and decontrol. The family, as has been said, is the basic social relationship. Here the child feels and experiences security, warmth, love, well-being, according as he is handled, or insecurity, fear, aloneness, tension, irritation, and anger. Unwise love, devotion, attention, protection, supervision, induce dependency, insecurity, fear, inferiority, lack of initiative, self-confidence, and courage. Not enough warmth, fondling, and tenderness lead to unresponsiveness, coldness, aloneness, and insecurity—the forerunners of schizophrenia. Bottle-fed babies, uncuddled, on rigid routines, with no concessions to human feelings, lead to feelings of isolation and rejection, which ultimately appear as the utter aloneness and seclusiveness of the schizophrenic patient. Too much control, suppression, domination, supervision, regimentation, and punishment leave the child devoid of personality, with doubt and indecision, or too much anger and revolt.

It is a question of balance. There should be enough love, devotion, and protection for security, but not too much to retard independence and growth. There should be sufficient direction and supervision, so the child obtains enough support to try new things, develop self-confidence, and initiative; but not too much to prevent the development of independent decision and self-direction. There should be enough discipline to learn the nature of the world—especially the social world with its expectations and demands; but not too much to produce crippling fear, resentment, or rebellion.

In the family, with the mother, father, and siblings, we learn to share, yield, postpone satisfaction, tolerate, coöperate and contribute. The child finds it difficult to share his clinging, dependent love (security) with his father (frustration, deprivation, discipline, punishment). In this emotional relationship, intense feelings are mobilized, of increased love—dependency demands (as compensations for loss and threat of loss); insecurity and fear, irritation, anger and hostility, envy, jealousy and guilt. The feelings of

security, warmth, and well-being, or of anxiety, tension, and hostility, aroused in relation to parental handling of the child, parental attitudes toward one another and toward the child—this vast complex of feeling relationships is what Freud meant by the *Oedipus Complex*. Rejection of the child by attitudes or subtly expressed feelings, undue lack of consideration for the child's needs and helplessness, undue deprivation, postponement of satisfactions, frustration, sternness, exactitude of toilet training, e.g., threats of or actual punishment—acts or attitudes that devitalize, that take away the normal power and adequacy of the child, or that deprecate his personality, and the associated feeling reactions of fear, envy, jealousy, resentment, hostility, discouragement, and inferiority, are what is meant by the *Castration Complex*.

On the resolution of these vast complicated complexes of feelings in the family relationship will depend the future stability of the personality or the predisposition to emotional (i.e., nervous or mental) illness. If the parent gives the proper amount of love, tenderness, support, guidance, and control—and not too much or too little—a child will not be unduly emotional, with its physiological counterparts. He will be able to defer, tolerate discomfort and tension, postpone satisfaction, share, coöperate, and contribute. His intellectual development will proceed normally, free to learn and apply skills appropriate to his age.

If the emotions are not guided, and conditioned wholesomely, the personality will be too emotional. The adult will have anxieties like the child who is insecure and fears being alone, or he will be phobic, like the child with panics at the sound of thunder or the sight of terrifying animals, or the adult will have hostilities and destructiveness like the tantrums of the child or depression like the rejected, deprecated, unprotected or overdominated child.

Psychoanalysis speaks of *fixation* when in infancy or childhood these emotions (love, parental dependency, fear, anger, depression) are excessively stimulated, so that in later life in the face of difficulties, unfair practices of others, situations requiring unusual effort and problems, old emotional thalamic patterns are revived and the patient regresses to the earlier, ineffective, unorganized, emotional reactions of early life. This is the meaning psychologically and developmentally of neurosis and psychosis. Just as in the decorticated animal there asserts itself overactivity of more primitive centers in decerebrate rigidity; so when the individual is psychologically overwhelmed or cortically disorganized, more primitive forms of emotional reaction appear.

Psychoanalysis has developed the concept of the *unconscious*. This is not a mysterious concept. It refers to phenomena where there is splitting, disconnection, or dissociation of processes that normally should be connected. It is lack of awareness of psychological (or conditioned) connections or relationships. For example, a patient said she had no temper or anger, yet had fears and impulses to break things. She did not recognize

the motivation or causes. She was not aware that the impulses to break things were related to her dissatisfactions and irritations (anger which she did not realize) with her husband. The things she felt like destroying were substitutes for the feelings toward her husband. There was here *substitution* of object and *displacement* of feelings. Similarly a woman had persistent, intractable, crippling pain in her back for several years. It was not relieved by orthopedic treatment. She was not aware that the pain was a displacement (conversion) of anger at her husband into muscle pain. These mechanisms of substitution, displacement, disconnection or *dissociation,* with lack of recognition of essential and causal relationships which are subsumed under the concept of the unconscious, make patients' reactions seem so often bizarre, unreasonable, and helpless before the ordinary processes of reasoning and will power.

The world of the neurotic and psychotic is personalized with the feelings and reactions that were directed as a child toward the parents in the family. That is why their reactions are so intense and personal. Psychoanalysis speaks of this process as *transference.* This is one explanation for the extraordinary devotion of patients toward doctors, and also patients' unreasonable bitterness and lack of coöperation.

In infancy and childhood, nutritive and eliminative satisfactions and discomforts with their physiological processes are dependent on the consideration, attitudes, and behavior of adults. The satisfaction of physiological hunger becomes equated with love, warmth, friendliness, and well-being. If there is a deficit of these psychological factors in infancy and childhood, there are often disturbances of the gastrointestinal functions. Later in life in the face of insecurity, difficulties, unfair consideration by others, deprivation, hostility and anger, the gastrointestinal functions will be disturbed and we call it a gastrointestinal neurosis. These functions have been sensitized in childhood by parental handling and discipline. In later life they are a more sensitive barometer to situations involving insecurity, deprecation, and frustration than the cortex. There will often be marked physiological disturbances by these factors before the individual is aware of the factors provoking the response. He is unconscious of them. It is as if the cortex is by-passed.

Another example may be given. Unusual exactitude in the demands of the parents in toilet training, precociously required before even cortical development of well coördinated muscular control has appeared, often has deleterious echoes in later life. It focuses undue attention (and stimulation) on the lower gastrointestinal tract. Parental pressure also creates resistance, resentment, hostility, and rebellion. In later life, in relationships or circumstances where people are normally demanding, dictating, controlling and frustrating, the former hostility and rebellion will be awakened. Such people have been conditioned, made sensitive or allergic to such recurrent situations. Again the lower bowel may be the first indicator or barometer of such relations. Disturbances of lower bowel function appear long be-

fore the patient is aware of the source of the difficulties. "Neurogenic" colitis may be appearing as the chief manifestation of resentment and anger. The personality and physiological organization of such individuals is what Freud meant when he spoke of an *anal character* or personality.

Hysterical characters are emotionally labile, with marked tendencies toward changeability, instability, reversibility, and increased predisposition toward physiological expression of emotions. A father was inconsistent. One minute he was adoring and indulging; the next minute he was dominating, punitive, rejecting, overwhelming, and hurting. The child's love, security, and creative impulses could not be organized. She was afraid the adoring one would suddenly change to the threatening one. So she had abnormal variations and fluctuations of fears, enthusiasms, loves, hates, depressions, and revolts. She was unable to move into a reasonably constant, loving, sharing, coöperating, contributing relationship with people. She could not become an adult psychologically because of the fixations or pressures forced on her by parental handling.

Psychoneurotic, psychosomatic (I prefer the term: functional medical conditions) and psychotic reactions, therefore, depend on or really are the expressions of the basic emotions of love and security, insecurity and fear, anger and hostility, and depression,—overwhelmingly conditioned, hyperstimulated, or inadequately expressed—in all their permutations, combinations, and distortions.

Life consists of a succession of circumstances where one must: make an effort, postpone or give up; attack or avoid; assert or submit; acquiesce or resist; dominate or defer; fight or withdraw; master or be defeated; express or restrain; survive or be destroyed; take or give; and other polarities. The resolution of these alternatives will depend on the basic thalamic instinctive organization or conditioning of the personality: the intensity and adequacy of our love-security, insecurity-fear, resentment-hostility, expansive-depressive make-up. The balance will be turned by the nature of these thalamic forces within us, more than by our cortex or reason. This organization is ultimately dependent, of course, on our heredity, physiology, and temperament, but functionally on the nature and the effect of parental conditioning of the child in the family situation—the results of the Oedipus and castration complexes in psychoanalytic terminology.

Sex, according to Freud, is popularly misunderstood. He broadened the concept. It is not limited in his conceptions to localized genital anatomy and genital function. Under sex he includes what most people think of by the words: love, interest, attraction, devotion, creativity, and the feelings and impulses related thereto, whether toward persons, money, causes, or scientific, literary, artistic, or social endeavors.

Therapy in psychoanalysis is devoted chiefly to relieving patients of crippling emotional tensions or hyperstimulations, and developing the patient's understanding of his pattern of personality organization and his

typical reactions to life situations. This is done chiefly through the process of free association, abreaction, and the interpretation of dreams and symptoms. *Free association* merely means talking of whatever comes to mind, and not having the content of the patient's remarks become directed by questions of the doctor. The latter is directed, controlled thinking. Free association expresses thoughts that come to mind however sporadic, unconnected, illogical, bizarre, or anti-social. By this process a sort of emotional gravitational trend of thoughts and attitudes comes into play and becomes apparent. The pattern of reaction becomes clear, as also its origin. That is the way one breaks through the irrational defenses and unreasonableness; whose source is not known to the patient. The rationality of symptoms becomes clear. The play of free association, of the apparently irrelevant, ultimately shows, to the patient, a logic beneath his symptoms, which is convincing.

In the play of free association there is frequently intense expression of violent emotion. This is called abreaction. It releases the patient from the crippling intensity of feelings, minimizes and desensitizes them. The unexpected intensity often focuses the patient's attention on relevant factors of which he had no awareness.

The insights and contributions of Freud have been epochal. Before his time psychiatry was classificatory, and treatment was expectant and custodial. Since his discoveries psychiatry has become etiological and dynamic, and therapy rational and psychological. His scheme of the development of the human personality has given us a paradigm by which we can understand much of the irrational, chaotic, and bizarre, seen in psychiatric conditions. Freud himself changed his formulations and that process is still going on with progressive thinkers in psychoanalysis.

Many patients, of course, cannot be analyzed—the majority of them for many reasons. But psychoanalytic insights are helpful in many conditions that cannot be analyzed. The psychoneuroses, some psychoses, and some psychosomatic or functional medical conditions, are those in which it may be employed.

The insights of psychoanalysis far transcend its therapeutic efficacy. The contribution of psychoanalysis as a method of investigating the human personality, as a tool of research, and as a means of insight, may very well turn out to be greater than as a method of therapy. But Freud's contribution has been basic and epochal in psychiatry. It has thrown light where there was darkness and confusion, and has brought order where we saw only chaos. It is like the introduction of the benzene ring in organic chemistry. It has made our thinking functional and dynamic rather than static and verbal. It has opened new realms in psychotherapy and made it rational. The extravagances and errors of observation and theory will be corrected by time and experience.

ESSENTIAL FAMILIAL HYPERCHOLESTEROLEMIA *

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THE metabolic disorder characterized by an increase of the total blood cholesterol with normal proportion of esters, and frequently an increase in the phospholipids, is designated by us as essential familial hypercholesterolemia. While this term does not follow the classifications proposed by Thannhauser,[1, 2] Montgomery,[3, 4] and others,[5, 33, 34] it is more descriptive and useful.

While many pathological conditions have been known to be associated with xanthomatous deposits in the skin, the significance of the primary metabolic disorder has not been fully recognized. Too much emphasis has been placed on xanthoma tuberosum, xanthoma tendinosum, and xanthelasma.

We were presented with a unique opportunity for the study of a familial condition. Not only were there four generations composed of 282 individuals available for investigation, but the various sibships were large and coöperative. Thorough clinical studies in 159 of these are used for statistical analysis. This group of 159 includes all individuals found to have elevated blood cholesterol, and many others with normal levels. The examinations are sufficiently complete to exclude the more common causes of hypercholesterolemia, such as nephrotic syndrome, diabetes, hypothyroidism, pregnancy, jaundice, and disease of the liver.

Our study included:

1. Medical history and physical examinations (rectal examinations were made only when suggested by the history; no vaginal examinations were done).

2. Urine was examined for albumin, sugar and urobilinogen. The sediment was examined if there was any albumin present.

3. Electrocardiograms were done on 21 of the group that had elevated blood cholesterols and on 11 of the normals.

4. Basal metabolic rates were determined if there was any suggestion of hypothyroidism.

5. Diet diaries were kept for a period of time. The results were analysed by competent dietitians and calculations of the cholesterol intake were made on 91 individuals.

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TABLE I

Blood Lipid Values

Individual	Age as of March 1947	Total Cholesterol	Cholesterol Esters	Phospholipids	Total Lipids
A–1	30	335	262	260	865
A–1x	26	210	152	183	579
A–2	29	355	230	283	870
A–2x	32	180	107		
A–3	25†				1383**
A–4	23†				1330**
A–5	23	335	209	265	770
A–5x	27	208		248	
A–6	22	213	105		
A–8	19	216	120		
A–9	25	325	280	184	631
A–6x	25	262	250		
A–12	14	254	171	195	482
A–13	12	394	281	312	807
A–14	11	700	505	413	1350
A–16	8	185	110	217	
A–17	3	550	537	357	756
A–18	1	381	281	325	645
A–4x	35	250	166		
A–9x	25	250	125		
B–1x	62	237			
B–2	53	194*	135	235	699
B–2x	52	229	140		
B–3	51	187	135		
B–3x	49	141	100		
B–4	50	216	160	320	727
B–5	47	262	156		
B–9	46	300	102		
B–6	43	217	122		
B–6x	36	200	122		
B–7	41	183	112		
B–7x	35	251	105		
B–8	38	370	254	245	759
B–8x	36	150	67	163	510
B–10	49	446	382	300	937
C–1	49	288*	204	291	869
C–12	59	248	142		
C–12x	58	175	110		
C–11	56	350	205	330	
C–11x	59	230	136	145	679
C–10	57	320	210	423	1086
C–9	56	210	130		
C–8	53	196	127		
C–8x	57	210	170	255	
C–7	51	153	98		
C–7x	49	225	175		
C–4	48	182	117		
C–5	44	412	285	520	1516
C–6	42	146	83		
C–6x	42	175	116		
C–3	40	420	350		
E–3	71	400	162	360	1000
G–1	80	161	98		
G–4	77	212	120		
H–4	31	196	141		
H–2	30	186	108		
H–2x	28	187	87		
H–3	29	312	162		
H–1	28	166	89		

TABLE I—*Continued*

Individual	Age as of March 1947	Total Cholesterol	Cholesterol Esters	Phospholipids	Total Lipids
H–1x	30	200	117		
I–2	28	251	112		
I–2x	28	220	135		
I–5	25	205	130		
I–6	22	126	80		
I–3	17	215	127		
K–1	30	180	147		
K–1x	35	223	153		
K–2	19	248*	181		
K–3	25	140	80		
K–4	20	283	131		
L–2	22	237	140		
L–7	10	158	98		
L–9	7	160	78		
L–8	7	166	93		
L–12	3	200	180		
L–10	2	187	93		
BA–1	17	201	123		
BB–1	14	215	120		
BB–2	13	251	103		
BB–3	9	251	110		
BB–4	7	220	140		
BB–5	5	237	100		
BC–1	10	271	141		
BD–2	6	190	99		
BD–3	4	425	287	445	1328
BD–4	3	187	93		
BE–1	7	187	112		
BE–2	4	237	170		
BF–1	4	415	218		
BG–1	4	316	175	258	975
BI–1	32	147	107		
BI–4	29	152	90		
BI–2	28	205	100		
BI–3	25	135	100		
BI–6	23	275	190		
BI–5	19	135	110		
BJ–1	34	169*	117		
BJ–2	32	141*	100		
BJ–3	31	200	179		
BJ–5	27	225	102		
BJ–5x	29	286	145		
BJ–6	25	133*	91		
BJ–6x	22	208	112		
BJ–8	23	151*	104		
BJ–9	21	188	102		
BJ–10	18	119*	75		
BJ–11	16	116*			
BK–1	34	433	268	373	1317
BK–1x	34	163	101	263	595
BK–2	32	210	162		
BK–2x	27	152	112		
BK–3	30	433	268	267	
BK–3x	32	175			
BK–4x	22	227	170	150	
BK–5	25	333	300	358	
BK–6	23	170	120		
BK–6x	21	204	125		
BK–7	22	337	262	350	1140
BK–8	20	205	110		
BK–9	19	188	101		

TABLE I—*Continued*

Individual	Age as of March 1947	Total Cholesterol	Cholesterol Esters	Phospholipids	Total Lipids
CA–3	21	140	79		
CB–4	29	193*	135		
CB–4x	23	175	127		
CB–2	27	215	188	225	
CB–3	26	210	112	217	
CB–3x	21	200	117	175	
CC–1	29	175	127		
CC–1x	25	155	117		
CC–2	26	165	135		
CC–3	24	169*	119		
CC–4	22	183	123		
CC–5	19	167	117		
CC–7	10	170	95		
CF–1	12	182	135		
CF–2	15	250	150		
CF–3	3	175	100		
CG–2	3	170	115		
CG–3	5	170	130		
CH–1	6	200	97		
CH–2	2	187	117		
CI–3	8	158	110		
CI–1	5	200	115		
CL–1	9	187	121		
CL–2	7	250	116		
DA–1	2	175	83		
DF–1	5	183	112		
DG–1	9	406	233	380	1239
DG–2	7	196	140		
DG–3	6	196	140		
DG–4	5	341	281	455	1412
DH–1	7	153	105		
DH–2	6	160	100		
DH–3	3	160	210		
DI–2	5	205	95		
DI–1	2	152	110		
DJ–1	3	142*	101		
DK–1	3	165	135		
EF–2	6	153	116		
EF–1	3	208	142		
FC–1	57	237	102		
FC–2	48	196	130		

* Schoenheimer-Sperry Method.
** Determined in 1928.[21]
† Age at death.

6. Total cholesterols and cholesterol esters were determined on all. Phospholipids and total lipids were determined on all of the individuals in whom the blood cholesterol was increased, and on many of the normals (table 1).

The Bloor [6] method for determining blood cholesterol was used in the initial survey because of the large number to be studied. The method was changed to the more accurate and time-consuming technic of Schoenheimer-Sperry [7, 8] when certain detailed metabolic studies, which are still under way, were begun. The values determined by the latter method are designated by an asterisk. Phospholipids were extracted and precipitated by the

method of Boyd,[9] and phosphorus was determined by the method of Fiske and Subbarow.[10] Total lipids and neutral fat were determined by the method of Boyd.[9] The correlation of the blood cholesterol levels with the genetic pattern of transmission revealed a clear-cut distinction between normal levels and abnormal elevation of the blood cholesterol (figure 1). We consider 280 milligrams per cent by the Bloor method and 210 by the Schoenheimer-Sperry method abnormal elevation. Only three of our normals (B–5, BC–1 and BJ–6) exceeded 260 milligrams per cent by the Bloor or 200 by the Schoenheimer-Sperry method.

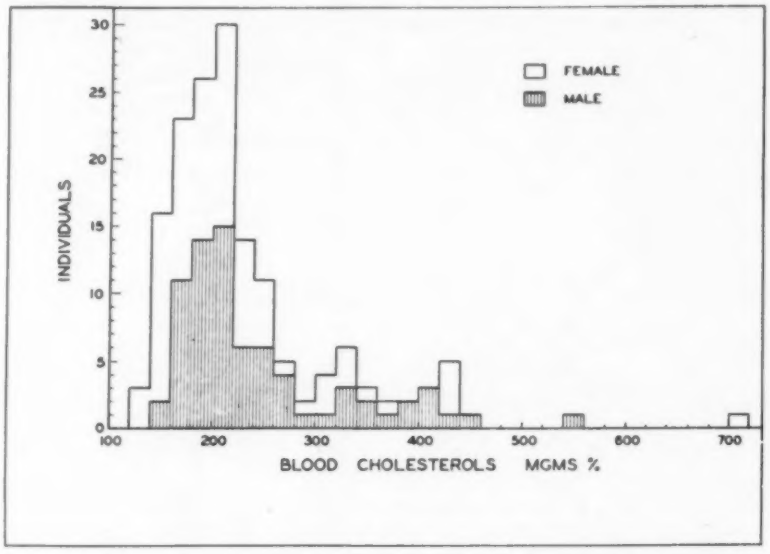

FIG. 1. Histogram of total blood cholesterols, plotted as Bloor values.

Many authors [11, 12, 13, 14, 15, 16, 17, 18, 19, 20] have pointed out that the condition under discussion is hereditary and several modes of transmission have been postulated. Svendsen [15] believes that increased cholesterol is a dominant trait. Müller [13] states that either xanthoma or increased cholesterol is a dominant, while Thannhauser and Schmidt [19] consider both recessive.

It is not difficult to understand these discrepancies when one realizes that it is rare to find reports in which two generations have been studied. Most of the reported families are small, or only a small number of the members was investigated. We have been able to study four generations of large families and to examine nearly all living members of most sibships.

It can be seen from the family tree (figure 2) that whenever one parent had an elevated blood cholesterol, approximately one-half of the children had an elevated blood cholesterol. This is shown to good advantage in sibships K and BK (figure 3).

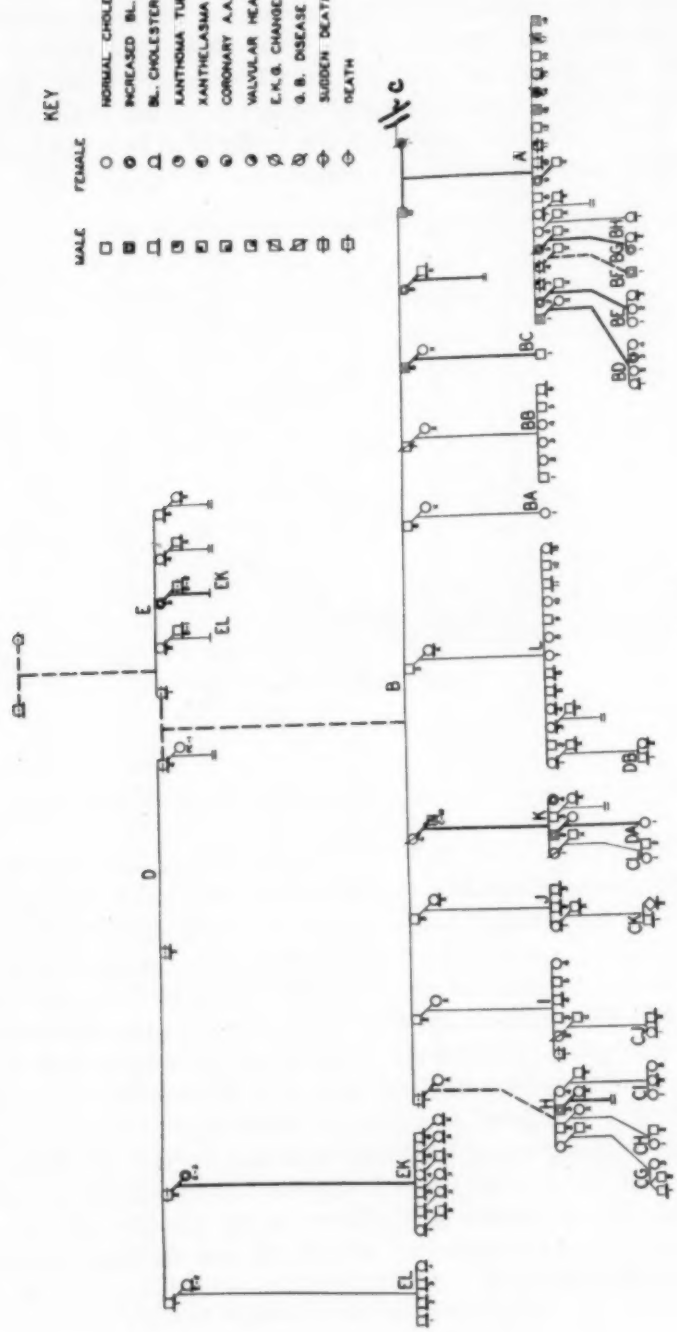
KEY
MALE
FEMALE
NORMAL CHOLESTEROL
INCREASED BL. CHOLESTEROL
BL. CHOLESTEROL UNKNOWN
XANTHOMA TUBEROSUM
XANTHELASMA
CORONARY A.A. DISEASE
VALVULAR HEART DISEASE
E.K.G. CHANGES
C. B. DISEASE
SUDDEN DEATH
DEATH
A
B
C
D
E
BA
BB
BC
BD
BE
BF/BG/BH
DB
EK
EL

FIG. 2A.

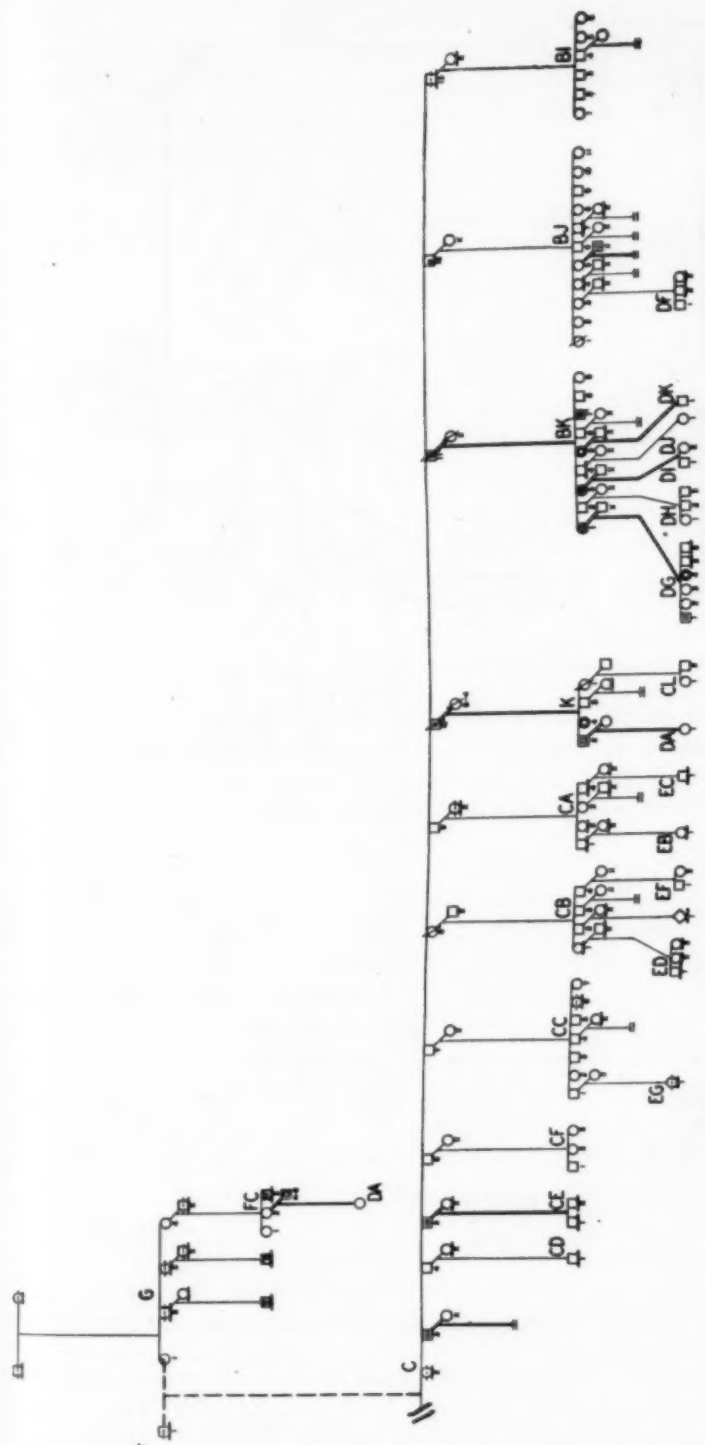

FIG. 2B.

FIG. 2A and 2B should be one continuous pedigree, but due to the large number of individuals involved, it has been necessary to split this into two figures. The two parallel lines at the end of Sibship B and Sibship C represent the point where the pedigree was broken. The heavy lines show the transmission of essential familial hypercholesterolemia. The heavy broken lines show presumptive transmission of this trait (i.e.) either both parents were unknown or one was normal and the other was unknown.

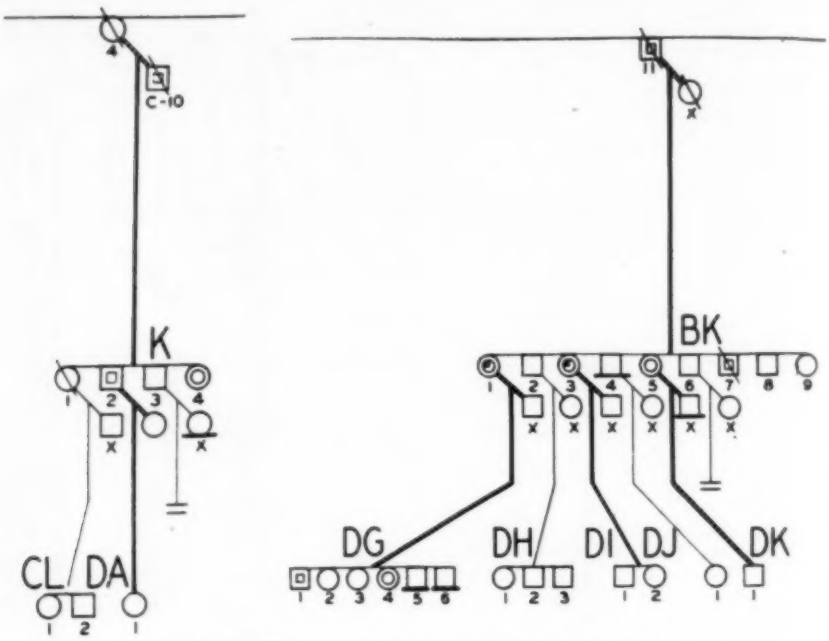

FIG. 3. Matings of heterozygous abnormal × homozygous normal.

When neither parent had an increased blood cholesterol, all of the children studied showed normal blood levels. (See sibships BB, BJ and CC, figure 4.)

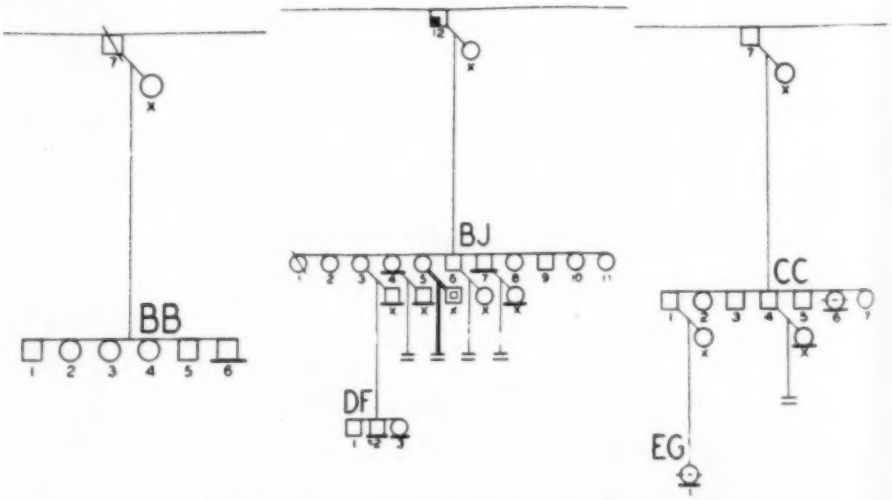

FIG. 4. Matings of homozygous normal × homozygous normal.

In the marriage of C–1 and B–10, both had an increased blood cholesterol. Of their 18 children (sibship A, figure 5), five had xanthoma tuberosum and/or tendinosum. Six had elevated blood cholesterol *without*

skin lesions and four had normal blood cholesterol. Three are reported not to have had skin lesions, but their blood cholesterol level is not known.

In the union of A–4 (who had xanthoma tuberosum) and A–4x (whose blood cholesterol was normal) the only child (BF–1) showed an increased blood cholesterol (figure 5).

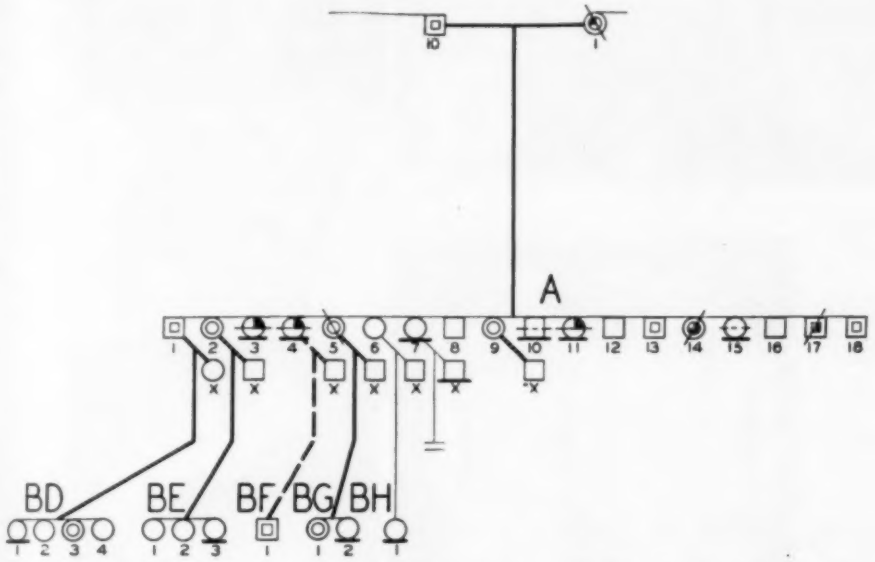

FIG. 5. Mating of heterozygous abnormal × heterozygous abnormal, and xanthoma tuberosum (presumed homozygous abnormal) × homozygous normal.

Of the five in sibship A who had xanthoma tuberosum and/or tendinosum (figure 6), only two (A–14 and A–17) were studied by us; but Curtis, Wile, Eckstein and Duemling [21, 22, 23] reported observation on two others (A–3 and A–4), and though blood cholesterols were not reported, these cases were typical clinically and pathologically. The family physician and parents report that A–11 was likewise typical.

It should be pointed out that there are two possible matings (homozygous abnormal × homozygous abnormal and homozygous abnormal × heterozygous abnormal) that we did not observe in this kindred. We feel, however, that our data are sufficiently complete and consistent to permit us to present a new theory concerning the mode of transmission (figure 7).

We postulate:

1. That the metabolic disorder characterized by increased blood cholesterol which is designated by "C" (as against a normal blood cholesterol designated as "c") is transmitted as a dominant.

2. Xanthoma tuberosum or tendinosum represents the homozygous abnormal.

3. A normal blood cholesterol represents the homozygous normal.

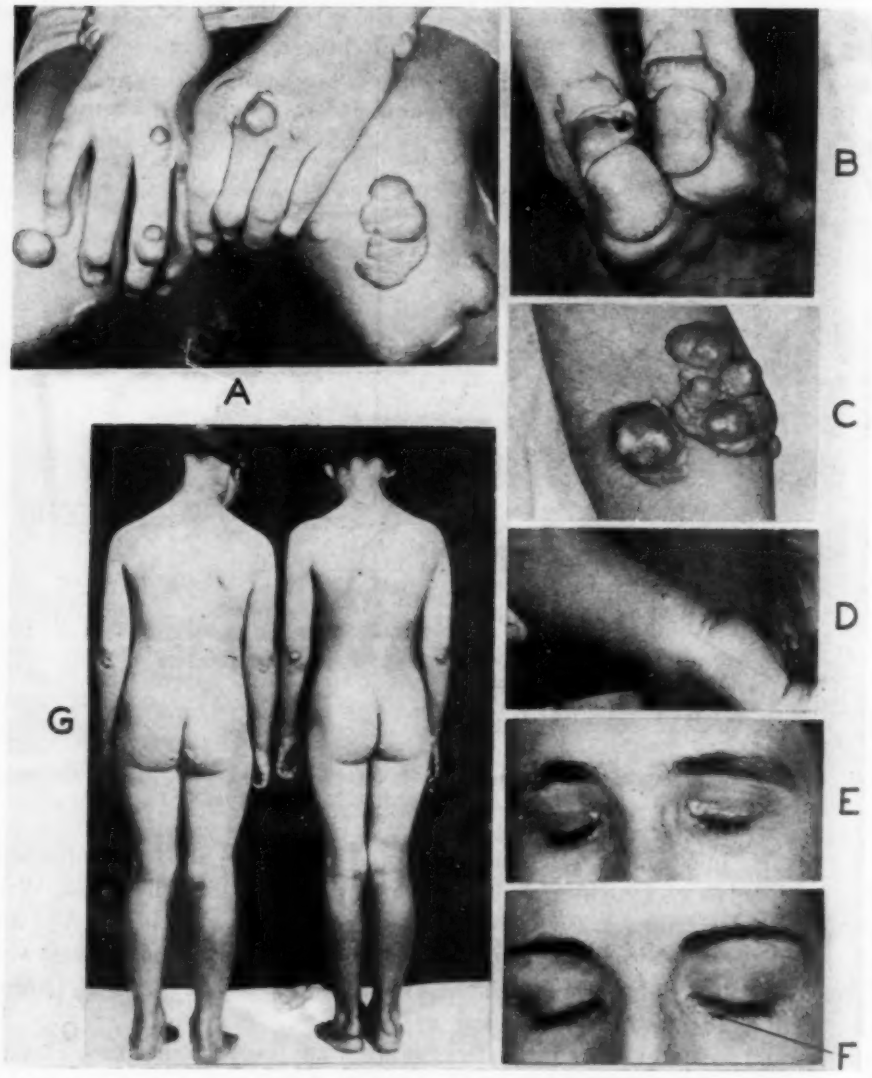

FIG. 6. A and C—Xanthoma tuberosum of A-14; B—Xanthoma tendinosum of A-14; D—Early xanthoma of A-17; E and F—Xanthelasmata of BK-1 and BK-3; G—Xanthoma tuberosum and tendinosum of A-3 and A-4.

This type of inheritance is known as "incomplete" [24] dominance because the severity of the condition is less in the heterozygote than in the homozygote.

A more detailed analysis of all the genetic data obtained will be presented by us at a later date and will include blood types and a number of test factors.[25]

The age incidence of the two groups is shown in figure 8.

It has been pointed out by many investigators [4, 14, 16, 17, 18, 26, 27, 28, 29] that certain clinical and/or anatomical abnormalities seem to be associated with xanthomatous deposits in the skin.

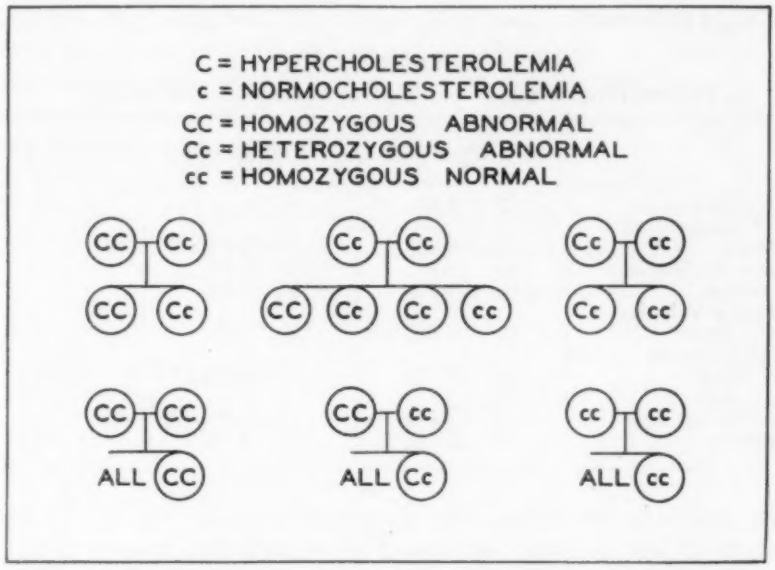

FIG. 7. Possible matings and predicted distribution of offspring.

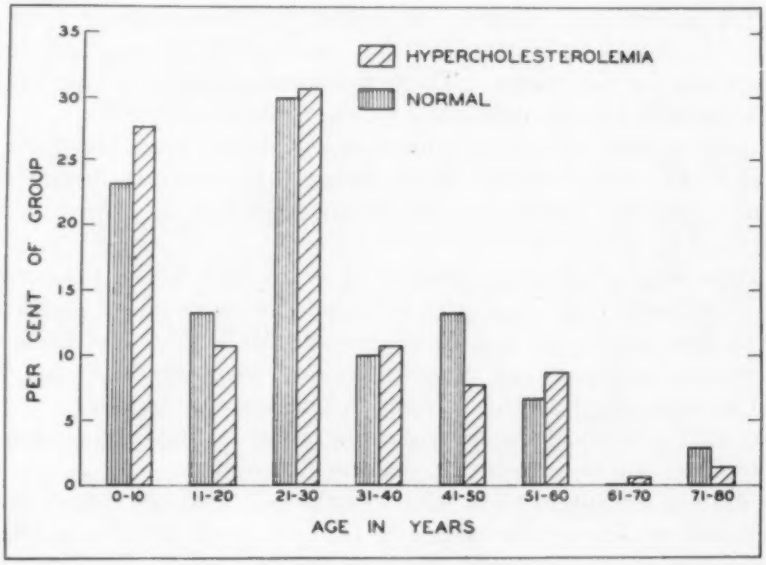

FIG. 8. Age incidence.

The relative frequency of these complications in essential familial hypercholesterolemia is shown in table 2.

It will be noticed that xanthoma tuberosum and/or tendinosum occurred in two of the hypercholesterolemic group, and they have been discussed.

Xanthelasma was present in three cases (C–1, BK–1 and BK–3) of the group with increased cholesterol, and in one case (G–1) in the group with normal blood cholesterol.

TABLE II

Relative Frequency of Clinical and/or Anatomical Abnormalities

	Hypercholesterolemia (30)	Normocholesterolemia (129)	Statistical Significance X'^2
Xanthoma {Tuberosum / Tendinosum}	(2) 6.6%	(0) —	—
Xanthelasma	(3) 10 %	(1) 0.8%	—
Arcus Juvenalis/Senilis	(0) —	(1) 0.8%	—
Angina Pectoris	(1) 3.3%	(1) 0.8%	—
Xanthomatous Valvular Heart Disease	(2) 6.6%	(0) —	—
Gall-Bladder Disease			
Clinical Story	(5) 17 %	(7) 5.4%	0.09
X-Ray Taken	(5)	(4)	—
X-Ray Positive	(2) 6.6%	(1) 0.8%	—
Heptomegaly	(5) 17 %	(3) 2.3%	0.01

Arcus senilis to our surprise was present in only one case (G–1) and here the cholesterol was normal. It should be pointed out, however, that a slit lamp was not used, as most of the examinations were done in the home.

Coronary artery disease as manifested by electrocardiographic changes and angina pectoris was found in one case of the hypercholesterolemic group (A–14). It should be emphasized that she was 11 years of age and had had symptoms for two years. There was one questionable case of angina in the group with normal cholesterol (C–12), his age being 59.

No diagnosis of myocardial infarction was made by us, but three (A–3, A–4 and A–11) died a sudden death before this study was begun; and as they had xanthoma tuberosum, infarction secondary to coronary atheromatosis must be suspected.[13, 14, 16, 18, 26, 27, 35]

Valvular heart disease was present in A–14 and A–17. There was no history of rheumatic fever, scarlet fever, or chorea in either of these children. In view of the fact that Montgomery,[4] Müller,[13, 14] and Cook et al.[35] have reported xanthomatous deposits on the valves of the heart, we feel justified in assuming that the valvular defects are due to them.

A detailed analysis of the electrocardiographic findings and cardiac status of this kindred will be presented elsewhere.[30]

We did not see any cases of biliary cirrhosis. Enlargement of the liver, however, was present in five cases (A–14, C–5, K–2, BK–7 and DG–1) of those with hypercholesterolemia and in three cases (K–1, BJ–2, and CB–2) of those with normal blood cholesterol. None of the eight gave a history of jaundice or had increased urobilinogen in the urine; hepatomegaly was unexplained.

A clinical story suggestive of gall-bladder disease was given in five instances (A–5, C–1, C–10, BK–7 and C–11) in the hypercholesterolemic group: cholecystograms, however, were positive in only two (A–5 and C–1). A similar story was obtained seven times in the normal group (B–4, B–7, C–8, I–2, K–1, BJ–1 and C–11). Except for three (B–7, C–8, and BJ–1), these were also x-rayed but only one (B–4) had a positive cholecystogram.

Hypertension was found in two cases with increased cholesterol (BK–7 and E–3) and in one case of normal cholesterol (B–4).

Splenomegaly was not found in this kindred.

The occurrence of secondary xanthoma in uncontrolled diabetes has long been known. It has been suggested by several authors [1, 21, 22, 23, 31] that there is some relation between primary xanthoma and diabetes, or at least a

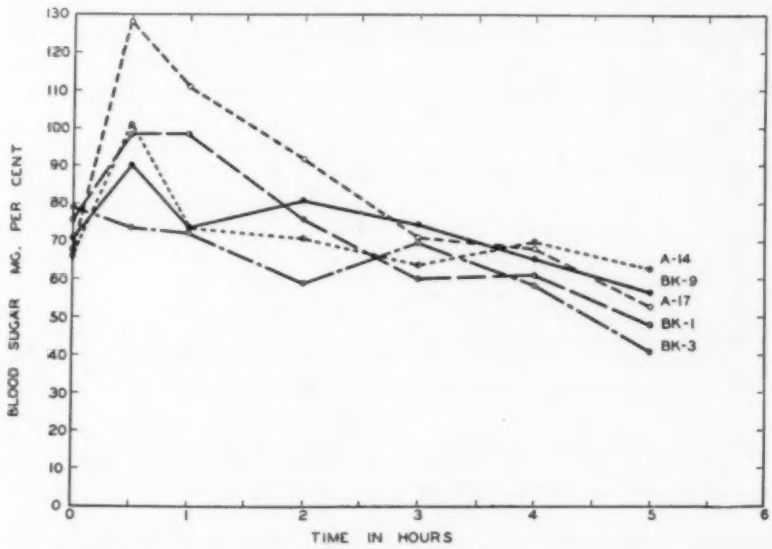

FIG. 9. Five hour glucose tolerance tests, showing normal utilization of carbohydrate.

decreased carbohydrate tolerance. Wile, Curtis, and Eckstein [21, 22] published so-called prediabetic glucose tolerance tests on two members of this kindred (A–3 and A–4). It must be pointed out, however, that these patients had been on a diet restricted both in carbohydrate and calories. In 1890 Hoffmeister [36] showed that a diabetic-like curve could be produced by starvation. Himsworth [32] has pointed out the necessity of properly preparing patients before doing a glucose tolerance test.

In view of the above, it was thought advisable to study the carbohydrate tolerance in this group.

Two patients with xanthoma tuberosum (A–14 and A–17) representing the homozygous abnormal; two patients with increased blood cholesterol and xanthelasma (Bk–1 and BK–3) representing the heterozygous abnormal; and one patient (BK–9) with normal blood cholesterol representing the

homozygous normal were placed on the standard University of Michigan glucose tolerance test preparatory diet (300 grams carbohydrate, 80 grams protein and 2800 calories) for three days, and then five hour glucose tolerance tests were performed (the dose of glucose being 1.75 grams per kilo of ideal weight). All of the five glucose tolerance tests (figure 9) were normal. There is, then, no reason to expect people with essential familial hypercholesterolemia to show an altered tolerance to carbohydrate if they have been properly prepared for the test. Individuals with xanthoma tuberosum, therefore, do not belong in the group of potential diabetics.

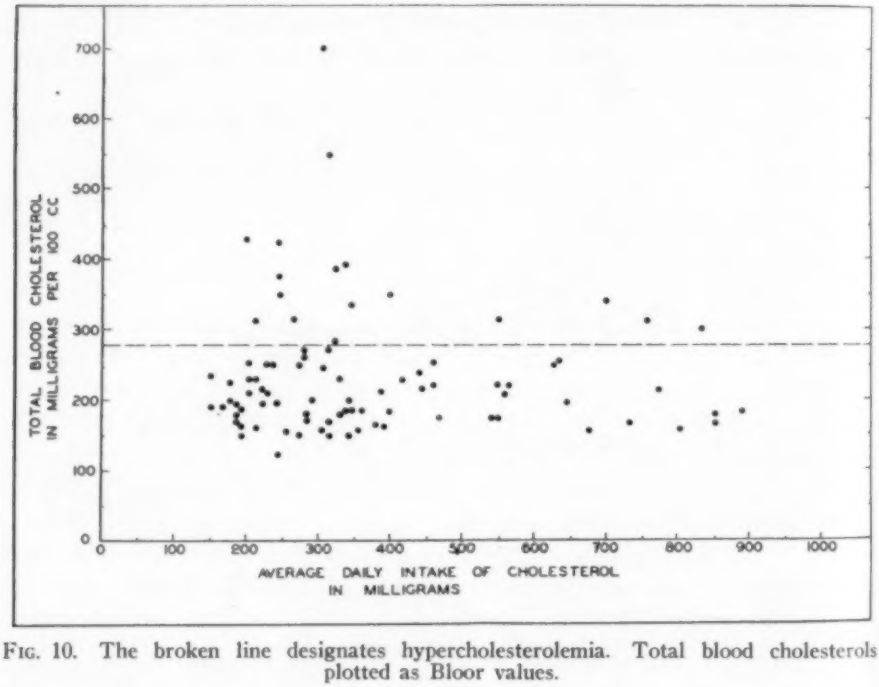

FIG. 10. The broken line designates hypercholesterolemia. Total blood cholesterols plotted as Bloor values.

As was mentioned above, an attempt was made to correlate the dietary cholesterol intake with the blood cholesterol. Figure 10 shows no association between the amount of cholesterol ingested and the blood cholesterol in either the normal or abnormal groups.

SUMMARY AND CONCLUSIONS

1. The metabolic disorder characterized by increased blood cholesterol is best described by the term essential familial hypercholesterolemia.

2. This condition is inherited as an "incomplete" dominant.

3. Xanthoma tuberosum represents the homozygous abnormal in this condition.

4. The upper limit of normal for blood cholesterols has been established by the genetic pattern of transmission.

5. The relatively greater incidences of certain pathological states in this condition, as compared with normal individuals is pointed out.

6. We were unable to demonstrate any delay in the utilization of carbohydrate in this condition.

7. The increase in blood cholesterol is endogenous, not dietary.

The authors are gratefully indebted to Dr. Fred H. Drummond of Kawkawlin, Michigan, who has observed this family for a number of years and, though too busy in the private practice of medicine to enter into this investigation, saw the value of such a study and was a constant source of information and encouragement.

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SUBJECTIVE MANIFESTATIONS OF THE HYPER-ACTIVE CAROTID SINUS REFLEX *

By Louis H. Sigler, M.D., F.A.C.P., *Brooklyn, New York*

It has been known for hundreds of years that pressure applied to the carotid sinus region may result in unconsciousness and convulsions. According to Ask-Upmark,[1] the Assyrians used this method to dull pain during the rites of circumcision. Perry [2] observed this phenomenon in 1779. The mechanism of its production, however, was not clearly understood until the pioneer work of Hering [3] and of Heymans.[4] These authors demonstrated that stimulation of the carotid sinus region results in a number of reflexes, the most prominent of which are those of cardioinhibition, vasodepression, and disturbances in respiration. This was followed by the work of other authors, notably that of Weiss and Baker,[5] Ferris and co-workers,[6] and Weiss and co-workers,[7] who demonstrated that unconsciousness and convulsions induced by the carotid sinus reflex were due in different individuals to stoppage of the heart or to a marked drop in blood pressure or to a direct cerebral effect.

In previous communications [8, 9] I showed in large groups of cases that the cardioinhibitory and vasodepressor reflexes occur most frequently and in greater degrees in older age groups, in males, and in arteriosclerotic heart disease.

This paper deals with the various subjective manifestations that may be elicited by the carotid sinus reflex and their relative frequency of occurrence.

Material and Methods of Study

The series consisted of 1,193 cases, made up of 750 males and 443 females. Their ages ranged between 15 and 75 years, the majority being over 35 years. Most of the cases were ambulatory office patients who had a greater or less degree of cardiovascular disease, mainly arteriosclerotic. Many had had one or more episodes of coronary occlusion in the past. There were also cases who suffered from other constitutional disturbances or from various forms of neuroses.

The test was performed in most cases in the sitting position, except in those who were bedridden. It was observed, as by Weiss and co-workers before, that in the sitting position the response was quicker and more pronounced. The head was extended backwards, and the carotid arteries at the level of the cricoid cartilage were located and were gradually compressed against the spinous processes. It is essential that pressure be exerted slowly and with progressively greater force, for in extremely hypersensitive persons comparatively little pressure may bring about alarming symptoms.

* Received for publication March 17, 1947.

TABLE I

Symptom Complexes Exhibited by Carotid Sinus Stimulation in Order of Frequency

Description of Symptom Complexes	No. of Cases	Per Cent of Those Responding	Per Cent of Entire Series Tested
Dizziness	62	6.4	5.2
Dizziness and inequality of pupils	49	5.1	4.2
Unconsciousness	40	4.1	3.4
Dizziness and flushing	32	3.3	2.7
Unconsciousness and convulsions	28	2.9	2.3
Unconsciousness and inequality of pupils	25	2.6	2.1
Dizziness and pallor, followed by flush, ipsolateral pupil dilated	24	2.5	2.0
Dizziness and cough	24	2.5	2.0
Confusion, dazed, and amnesia	23	2.4	1.9
Pallor	21	2.2	1.8
Dizziness and fainting sensation	20	2.1	1.7
Dizziness and weakness	19	2.0	1.6
Ipsolateral pupil larger	17	1.8	1.5
Dizziness and choking	16	1.7	1.4
Dizziness and fullness in head	16	1.7	1.4
Dizziness, pallor, fainting, and weakness	16	1.7	1.4
Unconsciousness, convulsions, flushing, pallor, and dizziness	16	1.7	1.4
Pallor followed by flush, darkness in eyes	16	1.7	1.4
Warmth in head	16	1.7	1.4
Dizziness and perspiration	15	1.5	1.3
Dizziness and darkness in eyes	15	1.5	1.3
Dizziness, marked weakness, fainting, and darkness in eyes	14	1.4	1.2
Electric shock, pupils dilated	14	1.4	1.2
Dizziness and warmth in head	13	1.3	1.1
Unconsciousness, dizziness, and pallor	13	1.3	1.1
Cough, pallor and flush	13	1.3	1.1
Blurred vision and general body warmth	13	1.3	1.1
Dizziness, cough, darkness of eyes, and slight warmth	12	1.2	1.0
Dizziness, cough, and darkness of eyes	11	1.1	0.92
Dizziness, flushing, nausea, spots before eyes, and clonic movements of extremities	11	1.1	0.92
Unconsciousness, sweating, dizziness, and dilated ipsolateral pupil	11	1.1	0.92
Dyspnea, warmth in head, headache	11	1.1	0.92
Fatigue	11	1.1	0.92
Dizziness and clonic contractions of local groups of muscles	10	1.0	0.84
Dyspnea and pallor	10	1.0	0.84
Tremors and weakness	9	0.9	0.75
Dizziness, flushing, darkness in eyes, fullness in head, and warmth in entire body	9	0.9	0.75
Unconsciousness, blurred vision, flush followed by pallor and ipsolateral pupil dilated	9	0.9	0.75
Unconsciousness, darkness in eyes, and tingling	9	0.9	0.75
Dyspnea, choking, heat in ipsolateral ear, and pallor	9	0.9	0.75
Warmth of body	9	0.9	0.75
Pallor, followed by flushing	9	0.9	0.75
Crying spell	8	0.8	0.67
Dizziness, weakness, and dyspnea	8	0.8	0.67
Dizziness, sensation of heat, stifling of breath, unsteadiness, and muscular incoördination	8	0.8	0.67
Dizziness and ipsolateral pupil dilated	8	0.8	0.67
Palpitation (premature contractions)	8	0.8	0.67
Dizziness, choking sensation, and dilated pupils	7	0.7	0.59
Dizziness, fainting sensation, numbness of lips, and inequality of pupils	7	0.7	0.59

TABLE I—*Continued*

Description of Symptom Complexes	No. of Cases	Per Cent of Those Responding	Per Cent of Entire Series Tested
Dizziness, darkness and pain in right eye, and blurred vision	7	0.7	0.59
Dizziness, sense of light in left eye, and pallor	7	0.7	0.59
Unconsciousness, convulsions, darkness, tingling, dizziness, weakness, palpitation, and dyspnea	7	0.7	0.59
Fainting and flashes before eyes	7	0.7	0.59
Flushing	7	0.7	0.59
Flushing and ipsolateral pupil dilated	7	0.7	0.59
Weakness and ipsolateral pupil dilated	7	0.7	0.59
Choking sensation	6	0.6	0.50
Nausea	6	0.6	0.50
Dizziness, nausea, confusion, general warmth, and ipsolateral pupil dilated	5	0.5	0.42
Dyspnea, cough, and faintness	5	0.5	0.42
Dyspnea and pain in head	5	0.5	0.42
Choking sensation and sense of heat in ipsolateral ear	5	0.5	0.42
Inequality of pupils	5	0.5	0.42
Pins and needles, numbness, and pupils larger	5	0.5	0.42
Dizziness, nausea, and palpitation	4	0.4	0.34
Dizziness and crying spells	4	0.4	0.34
Dizziness, noises in head, and blurred vision	4	0.4	0.34
Unconsciousness, crying spell, dyspnea, and flushing of face	4	0.4	0.34
Unconsciousness and dyspnea	4	0.4	0.34
Headache	4	0.4	0.34
Right pupil larger	4	0.4	0.34
Darkness in eyes	4	0.4	0.34
Dizziness and nausea and perspiration	3	0.3	0.25
Dizziness and lacrimation	3	0.3	0.25
Dizziness, weakness, and blurred vision	3	0.3	0.25
Unconsciousness and numbness	3	0.3	0.25
Tightness in throat and chest	3	0.3	0.25
Dyspnea, confusion, and weakness	3	0.3	0.25
Dyspnea and cough	3	0.3	0.25
Dyspnea, fatigue, and warmth in face	3	0.3	0.25
Blurred vision	3	0.3	0.25
Fatigue and belching	3	0.3	0.25
Pain in left ear	3	0.3	0.25
Tightness in chest and throat	3	0.3	0.25
Dizziness and warmth on side stimulated	2	0.2	0.17
Dizziness and vibrations in neck	2	0.2	0.17
Dyspnea, cough, and sense of bulging of eyes	2	0.2	0.17
Dizziness, pallor, and perspiration	2	0.2	0.17
Weakness in right face	2	0.2	0.17
Pallor, followed by flush and epigastric distress	2	0.2	0.17
Dizziness, crying spell, and dryness of tongue	1	0.1	0.08
Dizziness, weakness, dryness in mouth, pallor, and flush	1	0.1	0.08
Dizziness, and dead feeling in left hand	1	0.1	0.08
Dizziness, fear of falling, dyspnea, and ipsolateral pupil dilated	1	0.1	0.08
Choking, cough, pallor, and sense of swelling of tongue	1	0.1	0.08
Blurred vision, and pain of ipsolateral ear	1	0.1	0.08
Bitter taste, numbness	1	0.1	0.08
Stiffness of neck	1	0.1	0.08
Weakness, tingling of left hand, ipsolateral pupil dilated, cough	1	0.1	0.08
Pressure in head, ipsolateral pupil dilated	1	0.1	0.08
Tingling sensation hands	1	0.1	0.08

For the same reason, the test should be performed on one side of the neck at a time.

In cases where marked slowing or stoppage of the heart occurred, the pressure was continued until other symptoms developed. The same was true with the vasodepressor reflex. In cases where no cardioinhibition or vasodepression occurred, the carotid sinus compression was continued until all possible subjective disturbances could be elicited or until it was demonstrated that the individual was not to be affected. Usually, compression of one or the other carotid sinus for 15 seconds was sufficient to bring about all manifestations in the given individual, although some responded in four seconds and others required about a minute to exhibit the various manifestations.

TABLE II

Degrees of Cardioinhibition in Their Relation to the Frequency of Subjective Manifestations of the Carotid Sinus Reflex

Degrees of Cardioinhibition	Cases Showing Subjective Manifestations		Cases Showing No Subjective Manifestations	
	No. of Cases	Per Cent	No. of Cases	Per Cent
0	153	15.8	49	22.0
+	160	16.5	41	18.4
++	214	22.1	49	22.0
+++	198	20.4	46	20.6
++++	245	25.3	38	17.0

0, no cardioinhibition; +, less than 10 per cent slowing of the heart; ++, 10 to 30 per cent slowing of the heart; +++, 30 to 70 per cent slowing of the heart; ++++, stoppage of the heart for three seconds or more.

TABLE III

Incidence of Change in Blood Pressure in Relation to the Frequency of Subjective Manifestations of the Carotid Sinus Reflex

Blood Pressure	Cases Showing Subjective Manifestations		Cases Showing No Subjective Manifestations	
	No. of Cases	Per Cent	No. of Cases	Per Cent
Drop	674	69.5	132	59.2
No drop	257	26.5	75	33.6
Rise	39	4.0	16	7.2

To determine whether any relationship exists between the various subjective manifestations and the degrees of cardioinhibition, if present, the cases were divided into various grades of cardiac slowing, as follows: 0, indicating no slowing; 1 +, slowing less than 10 per cent; 2 +, slowing 10 per cent to 30 per cent; 3 +, slowing 30 per cent to 70 per cent; and 4 +, where the heart stopped for at least three seconds. To determine whether there is any relationship between the various subjective manifestations to vasodepression, the cases were divided into those that did and those that

did not show the various manifestations and each group was subdivided into those that did and those that did not show a drop in blood pressure.

Observations

Of the 1193 cases tested, 970, or 81.3 per cent, showed one or more subjective disturbances and often, also, abnormal objective findings in addition

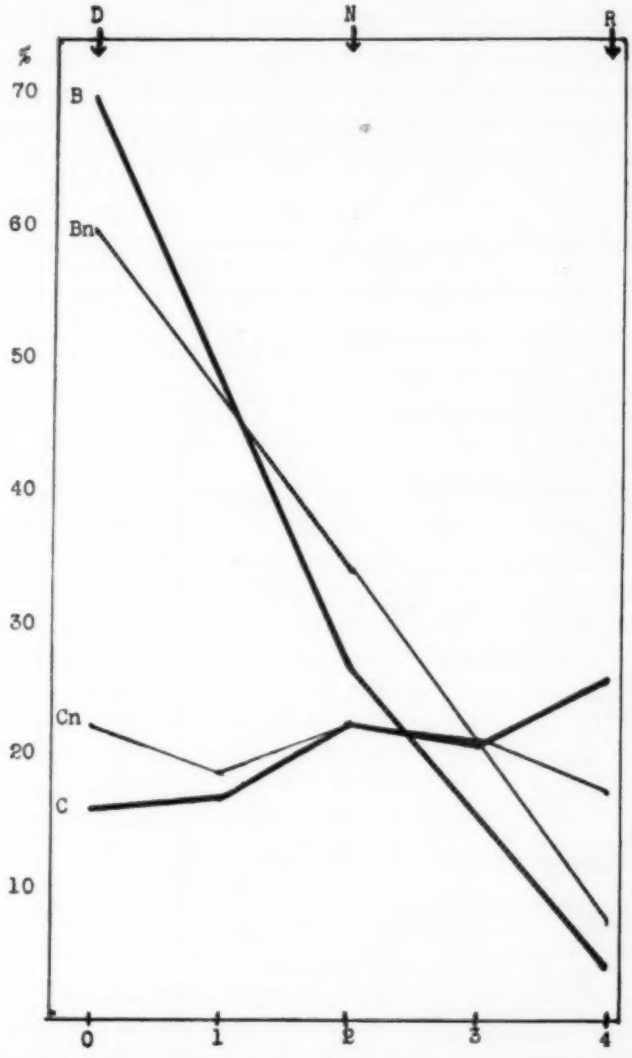

Fig. 1. Percental relationship of cardioinhibition, blood pressure changes and subjective manifestations. B and Bn, blood pressure curves in cases with and without subjective manifestations respectively. D cases with drop in pressure, N cases with no drop in pressure, and R cases with rise in pressure.

C and Cn, cardioinhibition curves in cases with and without subjective manifestations, respectively. 0, no cardioinhibition; 1, slowing less than 10 per cent; 2, slowing 10 to 20 per cent; 3, slowing 30 to 70 per cent; 4, stoppage of the heart for at least 3 seconds.

to cardioinhibition and vasodepression. In some cases there was only one complaint on the part of the patient, and in others two or more complaints or objective findings. The various manifestations were of diverse character and occurred singly or in various combinations in different individuals. Comparatively few cases exhibited exactly similar manifestations. All the symptoms were definitely more marked and more diverse in the older age groups.

In some, the abnormalities occurred upon pressure of the carotid sinus on one side and not on the other. In others, the same abnormalities developed upon pressure on either one or the other side in the same case, but to different degrees. In still others, some symptoms developed when pressing one side and other symptoms when pressing the other.

TABLE IV

Analysis of Individual Symptoms in Order of Frequency, Grouped under Disturbances of the Effector Structures of Organs

Organic Disturbances and Their Manifestations	No. of Cases	Per Cent of Those Responding	Per Cent of Entire Series Tested
I. Cerebral disturbances	822	84.7	68.8
Dizziness and related sensations	508	52.4	42.5
Unconsciousness	169	17.4	14.2
Fainting sensation	69	7.1	5.8
Confusion, dazed and amnesia	54	5.7	4.5
Crying spells	17	1.8	1.4
Noises in head	4	0.4	0.3
Fear of falling	1	0.1	0.1
II. Eye disturbances	394	40.6	33.0
Pupils unequal (ipsolateral dilated)	206	21.2	17.3
Darkness in eyes	85	8.8	7.1
Blurred vision, shine in eye	47	4.8	3.9
Both pupils dilated	26	2.7	2.2
Spots before eyes	11	1.1	0.9
Pain in eye	7	0.7	0.6
Lacrimation	3	0.3	0.3
Sense of bulging of eyes	2	0.2	0.2
III. Vasomotor disturbances	283	29.2	23.7
Pallor	108	11.1	9.1
Flushing	92	9.5	7.7
Pallor followed by flushing	43	4.4	3.6
Sweating	31	3.2	2.6
Flush followed by pallor	9	0.9	0.8
IV. Sensory disturbances	214	22.1	17.9
Sense of warmth, general, head ipsolateral side of face or ear	106	10.9	8.9
Pressure and fullness in head	32	3.3	2.7
Tingling and electric shock	25	2.6	2.1
Headache and pain in head	20	2.1	1.7
Numbness	19	2.0	1.6
Pins and needles	5	0.5	0.4
Pain in ipsolateral ear	3	0.3	0.3
Vibrations of neck	2	0.2	0.2
Dead feeling in hands	1	0.1	0.1
Stiffness of neck	1	0.1	0.1

TABLE IV—*Continued*

Organic Disturbances and Their Manifestations	No. of Cases	Per Cent of Those Responding	Per Cent of Entire Series Tested
V. Respiratory disturbances	171	17.6	14.3
Dyspnea	80	8.2	6.7
Cough	60	6.2	5.0
Choking sensation	23	2.4	1.9
Stifling of breath	8	0.8	0.7
VI. Somatic muscular disturbances	102	10.5	8.6
Generalized convulsions	74	7.6	6.2
Local tremors and clonic movements	20	2.1	1.7
Unsteadiness	8	0.8	0.7
VII. Constitutional disturbances (weakness-fatigue)	96	9.9	8.0
VIII. Gastrointestinal disturbances	38	3.9	3.2
Nausea	29	3.0	2.4
Belching	3	0.3	0.3
Epigastric distress	2	0.2	0.2
Dryness of tongue and mouth	2	0.2	0.2
Bitter taste	1	0.1	0.1
Sensation of swelling of tongue	1	0.1	0.1
IX. Cardiac abnormalities (aside from slowing or stoppage)	22	2.3	1.8
Palpitation due to premature contractions	19	2.0	1.6
Pain, tightness in chest and throat	3	0.3	0.3

The various symptom-complexes are shown in order of frequency in table 1. It will be observed that the most common are those of dizziness alone or in combination with other disturbances, followed in some cases by coma and convulsions. Some cases developed symptoms without marked slowing or stoppage of the heart or a drop in blood pressure. Alarming symptom-complexes, however, occurred most frequently among individuals who showed stoppage of the heart or a marked drop in pressure.

The numerical and percental relationships of the subjective manifestations to cardioinhibition and blood pressure changes are shown in tables 2 and 3 and in figure 1.

The various symptom-complexes observed were broken up into individual symptoms and classified in groups under the effector structure or organ. These are shown in table 4.

DISCUSSION

It will be observed that in the great majority of patients who seek medical attention for various conditions, a hyperactive carotid sinus reflex will induce various subjective and objective disturbances besides cardioinhibition and vasodepression. In our series of 1,193 cases, most of whom had some form of cardiovascular disease, 970, or 81.3 per cent, showed such disturbances.

The disturbances varied in their character and intensity, and occurred in different combinations. The most frequent were dizziness alone or in

combination with other symptoms. More severe disturbances which occurred next in frequency were complete unconsciousness, with or without convulsions. Some experienced mere confusion, amnesia, crying spells, and so on. Next in succeeding order of frequency were disturbances referable to the eyes, the vasomotor system, the sensory organs, the respiratory system, the muscular system, the constitutional state, the gastrointestinal system, and the heart.

The diversity of disturbances induced by the reflex speaks for a widespread distribution in the central nervous system of the afferent nerve impulses originating in the carotid sinus area.

It is of interest to observe that unconsciousness and convulsions, with the associated manifestations due to the carotid sinus reflex, occurred in some of our cases who never had spontaneous attacks. It was also observed that some patients who gave a history of one or more attacks of spontaneous dizziness, fainting, or unconsciousness not due to demonstrable disease of the central nervous system did not present these symptoms on carotid sinus pressure. Evidently reflexes originating in other parts of the body may produce the same cerebral manifestations.

Of the milder grades of symptoms of carotid sinus origin, many cases gave histories of spontaneous disturbances of the same nature. Others never experienced such disturbances until the test was applied. Still others gave a history of disturbances of like nature which could not be reproduced by the reflex.

A proper knowledge of the mechanism of the production of the various manifestations of the hyperactive carotid sinus reflex is of considerable importance, as it might elucidate the nature of symptoms in various disease states. The work of Weiss, Capp, and Ferris has helped to clarify the mechanism of the unconscious states and convulsions induced by this reflex. They have demonstrated that this syndrome is caused by cerebral ischemia due to cardiac asystole, extreme drop in blood pressure or to a direct cerebral effect, probably cerebral angiospasm. In some cases only one factor may be operative; in others, two; in still others, all three.

Judging from our findings, the direct cerebral factor appeared to occur fairly frequently. In many cases fainting and unconsciousness, with or without convulsions, occurred without stoppage of the heart or a marked drop in pressure. In others, where the stoppage of the heart had occurred, unconsciousness developed after the heart had returned to a normal or even faster than normal rate. In these cases, therefore, the manifestations were evidently caused by a direct reflex effect on the brain, producing either cerebral vascular spasm or changes in the synapses of various neuron connections. It appears that the health of the blood vessels supplying the brain is an important factor in the production of the cerebral manifestation. Individuals who suffered from cerebral arteriosclerosis showed the most alarming cerebral symptoms.

The various forms of response to the carotid sinus reflex speak against the possibility that hypersensitivity of the carotid sinus itself is responsible for the reflex reactions, unless we postulate the theory that the carotid sinus receptor organs are end organs of nerve fibers leading to different areas of the central nervous system in different individuals. Such wide anatomical variation is hardly possible. It is more likely that the variability in the reactions is dependent upon the sensitivity of the synaptic connections in the central nervous system, and upon the sensitivity of the various effector nerves or their endings in the effector structures or organs in different individuals. The reflex may therefore be used as an index in some cases of the functional state of these various parts of the central neurons, the efferent arms of the arc, or of the effector organ.

If, as it appears, the hypersensitivity is in the central neurons or in the efferent arm of the arc, therapy directed to the carotid sinus region alone must have great limitations. In cases where unconsciousness and convulsions occur as a result of comparatively little carotid sinus stimulation, such as by bending the head or by the pressure of a tight collar, and where the syndrome can be easily reproduced by comparatively little pressure on the carotid sinus, good results may be expected from surgical extirpation of the nerve connections in the carotid sinus region. Although this procedure will not alter the inherent sensitivity of the central neuron connections or the efferent arms of the arc, it will remove the impulses arising from the carotid sinus region. This appears to be substantiated by the result of operation on 13 cases by Craig and Smith.[10] They obtained excellent results in four cases, good results in one, fair in four, and poor in the rest. In cases where no spontaneous attacks occur and disturbances arise only as a result of stimulation of the carotid sinus, or in cases where manifestations like those arising from the carotid sinus reflex occur and cannot be reproduced by carotid sinus pressure, operative interference is useless.

A word of caution must be given in performing the carotid sinus reflex test. Inasmuch as the most severe reactions occur in the presence of cerebral arteriosclerosis, great care must be exercised in performing the test in the presence of this condition. Marmor and Sapirstein[11] have reported a case of bilateral thrombosis of the anterior cerebral artery following carotid sinus stimulation. Askey[12] reported seven cases of contralateral hemiplegia following carotid sinus pressure. I have encountered several instances of transient palsies and speech disturbances following carotid sinus stimulation. In two cases, complete hemiplegia occurred. All these cases had marked evidence of cerebral arteriosclerosis.

Summary

In 1,193 cases tested for hyperactivity of the carotid sinus reflex, 970, or 81.3 per cent, showed various subjective disturbances, besides cardioinhibition and vasodepression. In order of frequency, they consisted of dizziness,

unconsciousness and convulsions, abnormal sensation referable to the eyes, the vasomotor system, the sweat glands, the organs of sensation, the respiratory system, the somatic muscular system, the general constitutional state, the gastrointestinal system, and the heart. Individuals of the older age groups, especially those with cerebral arteriosclerosis, showed the greatest number and degrees of disturbances.

Many individuals who exhibited the various manifestations on carotid sinus pressure did not suffer from spontaneous attacks. Some individuals who experienced spontaneous attacks did not develop such attacks on carotid sinus pressure. In still others, carotid sinus pressure reproduced the symptom-complexes which the patient experienced spontaneously or as a result of bending the head or other irritating factors in the carotid sinus region.

The underlying physiologic disturbances responsible for the various manifestations of the hyperactive carotid sinus reflex appear to occur in the central neurons or in efferent arms of the reflex arc, not in the carotid sinus receptors. For this reason, surgical removal of the nerve connections of the carotid sinus region cannot be expected to relieve many cases, and whatever good results it may yield may not be permanent. It should be employed only in extremely serious cases of unconsciousness and convulsions which may be reproduced by the lightest pressure effect on the carotid sinus.

Inasmuch as very serious complications may develop as a result of the test in individuals with cerebral arteriosclerosis, great caution must be used in performing the test in such individuals.

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PENICILLIN TREATMENT OF STREPTOCOCCAL PHARYNGITIS *

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DURING recent years the commonplace and ubiquitous entity of "streptococcus sore throat" has been the object of intensive study. Interest in hemolytic streptococcal pharyngitis has been heightened both by its importance as an acute epidemic disease during the war, and by its current recognition as a primary excitant of rheumatic fever and glomerulonephritis. Coincidentally, the discovery of effective antistreptococcal agents has aroused interest in the treatment of the acute disease and the prevention of its sequelae.

The critical appraisal of any treatment demands the establishment of strict control groups and accurate delineation of the natural history of the disease in question. Survey of the current literature discloses no study of streptococcal pharyngitis in which a strict control group was established without regard for the severity of the presenting illness. Analysis of the course of the penicillin-treated disease has often been complicated by the concomitant administration of salicylates or sulfonamides.

An epidemic of streptococcal pharyngitis at a large, permanent army post provided an opportunity for the systematic study of the effects of treatment on the course of this disease. The epidemic was caused by group A hemolytic streptococci, largely types 19 and 23.§

During a 60 day period in the spring of 1947, 184 patients received a preliminary clinical diagnosis of streptococcal pharyngitis and were placed in special study groups at the time of their admission to the post station hospital. The objectives of the study were:

(1) To delineate the natural history of this epidemic of streptococcal pharyngitis in a young adult male population; (2) to assess the value of two methods of penicillin treatment as compared with purely symptomatic therapy; (3) to determine and evaluate the antistreptolysin response of patients in each of the three treatment groups.

The present report will be concerned mainly with the natural history and the results of treatment of streptococcal pharyngitis. Evaluation of the antistreptolysin response has been reported in a previous paper.[1]

Plan of the Investigation. The plan of the investigation together with a description of the bacteriological and serological methods used has been detailed in a previous article [1] and will be only summarized here.

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§ Typings were obtained on 80 patients (62.2 per cent); of these 56 were type 23 and 24 were type 19.

a. Selection of Patients. One or both of the investigators personally examined in the hospital receiving office virtually all patients admitted with fever or complaints referable to the upper respiratory tract during a period when 516 cases of upper respiratory infection were admitted to the hospital. A preliminary clinical diagnosis of streptococcal pharyngitis was made in 184 cases, and these patients were assigned in approximate alternate rotation to one of several study wards. Notations of the pertinent physical findings were made by the authors on worksheets especially designed for this investigation. Patients who manifested a scarlatiniform rash were considered to have a more serious disease (in agreement with Spink [2]), and were usually treated according to one of the two penicillin treatment schedules. They are not considered in comparing the untreated and treated groups, since most cases of scarlet fever received specific therapy.

At the beginning of the study 54 patients clinically diagnosed as streptococcal pharyngitis were treated with customary penicillin dosage consisting of 20,000 to 50,000 units every three hours for periods varying from four to seven days. Subsequently, the remaining 130 patients were dispatched alternately to one of two study wards; one group to receive penicillin, and the other, no specific treatment. With the exception of 11 patients with scarlet fever and two suffering from peritonsillar abscess at the time of admission, separation of patients into "treated" and "untreated" categories was effected without regard for the severity of the disease. Ward officers on the "untreated" wards were not permitted to initiate penicillin, sulfonamide, or salicylate therapy without consulting one of the investigators.

b. Definitive Diagnosis and Selection of Patients. A report by the Commission on Acute Respiratory Diseases [3] has implied that the definitive diagnosis of streptococcal pharyngitis is dependent upon the demonstration of anti-streptococcal antibodies during convalescence. In contrast, Rantz et al.[2] have stated that infection by streptococci cannot be excluded on the basis of the study of these antibodies (i.e. antistreptolysin and antifibrinolysin) since 10 to 20 per cent of scarlet fever patients may fail to exhibit an antibody response. Studies by Weinstein and Tsao [4] and more recently by Kilbourne and Loge [1] have demonstrated that penicillin treatment of scarlet fever or streptococcal pharyngitis may prevent the usual antistreptolysin response observed in these diseases. Thus, an important criterion for the diagnosis of streptococcal disease is of limited use in the evaluation of patients treated with penicillin. The following, exacting criteria were established for the final inclusion of patients in the study to be presented, regardless of how "typical" the clinical picture had been at the time of admission. The criteria were: (1) fever greater than 100° F. on the day of admission; (2) predominating growth of beta hemolytic streptococci on the initial throat culture; and (3) an admission total leukocyte count greater than 10,000 cells per cu. mm.

The few cases which have been included which did not necessarily fulfill all three of these criteria were cases in which: (1) a significant antistreptolysin rise was demonstrated; (2) the patient had a scarlatinal rash; or (3) peritonsillar abscess from which streptococci were cultured existed at the time of admission.

Application of the criteria plus the loss of patients by transfer and incomplete laboratory data reduced the series from 184 to 127 patients. The high proportion of patients (84.3 per cent) in the "untreated" group who exhibited a significant antistreptolysin rise is evidence of the accuracy of the preliminary diagnostic impressions.

c. Methods of Treatment. "Untreated" Group—The patients in this group received symptomatic therapy in the form of hot saline gargles or irrigations, obligatory bed rest for three days, and codeine when necessary. Salicylates were specifically interdicted in order to permit accurate observation of fever duration. All patients were closely watched for the development of complications. Two who developed peritonsillar abscesses were started on penicillin therapy and eliminated from this group.

"Treated" Groups—The patients in these groups received the symptomatic therapy outlined above, including the obligatory period of bed rest. In addition, they received treatment with one of two penicillin regimens, which for convenience will be denoted penicillin I, and penicillin II.

Penicillin I—This schedule entailed a single daily injection of 300,000 units of penicillin in aqueous solution for six or seven days. This dosage was selected as an amount which would maintain detectable concentrations (more than .078 unit per c.c.) in the blood for five to seven hours, an appreciable fraction of the 24 hour period.[5]

Penicillin II—Patients in this group received penicillin in dosages comparable to usual experience: 20 to 50,000 units every three hours for from four to seven days. Most of the patients so treated (75 per cent) received penicillin for six or more days. The average period of therapy was 5.6 days, and the usual individual dose was 30,000 units. It was anticipated that this regimen would provide almost continuous effective blood concentrations against the hemolytic streptococcus. Rammelkamp and Kirby state that 20,000 units of penicillin "produce concentrations having maximal antistreptococcal action for a period of more than two-and-one-half hours with partially inhibitory levels for another one-and-one-half to two hours." [6]

d. Laboratory Procedures. The following studies were made of each patient, usually within 24 hours of admission: (1) total leukocyte count; (2) urinalysis; (3) chest roentgen-ray; (4) Dick test; (5) antistreptolysin titer; (6) throat culture.

The leukocyte counts were repeated on the fourth and ninth days, urinalysis and Dick tests on the ninth day; throat cultures on the fourth, ninth and twenty-first days, and the antistreptolysin titers were determined again on the twenty-first day following admission.

Observations and Results

The Nature of the Presenting Illness. Hemolytic streptococcal pharyngitis as seen at Fort Monmouth in the spring of 1947 was an acute, febrile illness characterized almost invariably by throat soreness and frequently by moderate prostration. The illness was differentiated clinically from other endemic respiratory tract diseases by its more abrupt onset, the primary complaint of "sore throat," and the greater degree of prostration evident in its victims. Shaking chills and vomiting, although seen in less than one quarter of the patients, were evidences of toxicity of great value in differential diagnosis.

A surprising number of patients (82.9 per cent) complained of headache. This was usually frontal, but was sometimes occipital or generalized. Meningismus was occasionally simulated by posterior nuchal pain and soreness.

More than one-half of the patients complained of some degree of nasal congestion, but this was rarely a primary complaint. One-fifth of those with streptococcal pharyngitis suffered from pain in the extraocular muscles ("aching eyes"). Cough and hoarseness were rarely encountered.

Physical examination of patients in the receiving office was limited to measurement of the oral temperature, inspection of the skin, careful inspection of the pharynx, and palpation of the neck. Patients were usually seen on the first day of illness, as no penalty was attached to hospitalization.

and dispensary officers were ordered to hospitalize all febrile patients. Thus, the physical signs recorded below are truly indicative of the early acute disease.

Fever was usually present on admission, and exceeded 102° F. in almost 70 per cent of patients. Eighteen patients (14.1 per cent) presented themselves with scarlatiniform rashes. These cases were diagnosed as scarlet fever and are not utilized in this portrayal of the natural history of uncomplicated streptococcal pharyngitis. The incidence of rash varies with the erythrogenic potency of the infecting streptococcus [7] and therefore is a variable in any epidemic.

TABLE I

The Natural History of Streptococcal Pharyngitis

Symptoms	%	No.*	Signs	%	No.*	Course (Untreated)	Days	No.*
Sore Throat	98.6	77	Pharyngeal Injection	100	83	Fever Duration	2.6	45
Headache	82.9	74	Fever	99.1	127	Local Symptom Duration	3.8	27
Prostration (moderate or severe)	59.9	44	Uvula Edema	86.7	83	Systemic Symptom Duration	3.8	30
Abrupt Onset	58.4	77	Cervical Lymphadenopathy	81.8	82	Physical Signs (duration)	4.1	20
							No.	
Nasal Congestion	58.4	77	Coexistent Cervical Adenitis and Tonsils	74.6	67	Pyogenic Complications	4	51
Shaking Chill	26.0	76	Pharyngeal Edema	74.7	83	Late Sequelae	2	51
Aching Eyes	22.0	72	Tonsillitis (incidence of tonsils)	70.0	127	"Late Fever" (after febrile period)	11	45
Vomiting	17.5	74	Confluent Exudate	60.2	83	Reinfections or Relapses	0	51
			Scarlatinal Rash	14.1	127			

* Indicates the total number of patients yielding adequate data relative to each point.

A cardinal sign was the cautious manner with which patients opened their mouths for examination, illustrating dramatically the *soreness* of the pharyngeal and peripharyngeal tissues. Pharyngeal injection was present in all patients, and was usually classified as being of moderate or severe intensity. The commonest sites of erythema were the soft palate and anterior pillars, and the tonsils, when present.

Obvious pharyngeal edema occurred in three-quarters of all patients and proved a valuable diagnostic sign. Edema of the uvula was present in more than 86 per cent of the group, and when pronounced, was almost pathognomonic of streptococcal infection. As emphasized by Rantz and his associates [2] it was found that edema and erythema are valuable and characteristic evidences of streptococcal pharyngitis.

Tonsillitis was noted in 70 per cent of the cases, and, as would be anticipated in the presence of contiguous pharyngeal infection, occurred in all patients with tonsils. In these patients diagnosis was aided by the more obvious erythema and edema, and the more extensive exudate.

Confluent exudate was observed in only 60 per cent of patients, although its presence is emphasized in classical descriptions of streptococcal sore throat. Cervical lymphadenopathy was a frequent finding (81.8 per cent) and was most often manifest in the tonsillar nodes. In the absence of tonsils, tender adenopathy was of value in differential diagnosis. It was not observed, however, that tonsils acted as a "barrier" to inflammation of the cervical tissues, as three-quarters of those with cervical adenitis had tonsils.

The signs and symptoms of the disease together with the course of the untreated illness are summarized in table 1.

The Comparative Effects of Treatment

The effect of three treatment schedules on the course of streptococcal pharyngitis will be compared with respect to the duration of the acute illness, the incidence of complications and late sequelae, the relapse or reinfection rate, and the persistence of the carrier state.

The duration of the acute disease can best be measured by determination of the persistence of symptoms and abnormal physical findings, including fever. In the present study, information regarding signs and symptoms was obtained by questioning and reëxamination of the patients on approximately the fourth day of hospitalization (which was also usually the fourth day of illness) by one of the investigators. In an effort to obtain uniformity in the interpretation of signs and symptoms, reliance was placed only upon the observations or notations of the present investigators, except in the case of several of the earlier patients who received penicillin treatment II (see table 2).

In calculating the average duration of symptoms and signs, notations of i.e. "less than four days" have been given the mathematical value of four, spuriously implying an illness of longer than actual duration. In the small proportion of cases in which symptoms and signs persisted for more than four days, the exact duration of the illness was not determined, but such duration has been indicated merely as being "more than four days" (see table 2). Patients with protracted illness were categorized as having complications, sequelae or relapses of the acute disease and are discussed separately.

The comparative results of treatment are consolidated in table 2.

Fever Duration. The duration of the temperature response is probably the best single guide for determining the span of an acute febrile infection. Certainly, the frequency with which the body temperature is measured provides sharp definition of fever duration. Measurements of oral temperature were recorded usually four times daily, and occasionally every four hours. The duration of fever has been calculated and expressed in half days. Any day on which a temperature of greater than 98.6° F. has been recorded has been considered a day of fever unless such an elevation occurred only in the morning; in this event fever has been judged to persist for a "half

TABLE II

The Comparative Effects of Treatment

	Untreated		Penicillin I (300,000 units q.d.)		Penicillin II (20–50,000 units q3h)	
		No.*		No.*		No.*
Fever Duration (days)	2.6 days	45	1.7 days	33	2.0 days	24
(Patients with Rash) Fever Duration (days)	2.5 days	1	3.0 days	11	3.6 days	4
% with "Late Fever" (after 48 hr. afebrile period)	24.4%	45	16.6%	30	7.4%	27
Duration of Local Symptoms (days)	3.8 days	27	3.4 days	24	(4.2)**days	29
% of Patients with Local Symptoms longer than 4 days	17.2%	29	8.7%	23	—	—
Duration of Systemic Symptoms (days)	3.8 days	30	3.4 days	22	(4.4)**days	29
% of Patients with Systemic Symptoms longer than 4 days	3.5%	28	4.5%	22	—	—
Duration of Physical Signs (days)	4.1 days	20	4.3 days	18	—	—
% of Patients with Physical Signs longer than 4 days	37.0%	25	42.0%	19	—	—
Pyogenic Complications (number)	4	51	2	47	0	29
Late Sequelae (number)	2	51	3	47	0	29
Relapses or Reinfections (number)	0	51	2	47	3	29
% of Patients with Initial Leukocytosis	82.6%	46	93.5%	31	82.6%	23
% of Patients with Leukocytosis on 4th day	38.2%	34	25.8%	31	21.0%	19
Patients with Pred. Growth Beta Strep. on 1st Culture	100.0%***	47	100.0%***	40	100.0%***	27
% of Patients with Positive 4th day Culture	90.0%	40	37.4%	37	0.0%	19
% of Patients with Positive 9th day Culture	85.3%	41	53.5%	28	22.0%	9
% of Patients with Positive 21st day Culture	67.5%	37	35.2%	34	27.3%	22
% of Patients with Significant Antistreptolysin Response	84.3%	51	63.8%	47	13.8%	29

* Indicates the total number of patients yielding adequate data relative to each point.
** See text. (Duration of systemic symptoms).
*** Does not imply that all patients had positive initial culture. Only those with positive initial cultures were used in following the bacteriology of the pharynx.

day." Afebrile periods of less than 48 hours have been counted as febrile days.

Inspection of table 2 reveals no marked differences in the average fever duration in the three groups of patients, although the tendency to a slightly shorter course in the penicillin-treated patients is obvious. Detailed analysis of temperature charts, however, disclosed important differences between penicillin-treated and untreated patients (figure 3). Defervescence occurred in two days or less in more than 93 per cent of patients receiving intermittent

penicillin in large doses (penicillin I), and in almost one-half of this group (46.6 per cent) the pyrexia lasted but one day. More than two-thirds of the group treated with penicillin II were afebrile before the third day, but only 40 per cent of untreated patients.

In most cases fever had terminated by the fourth day, even in the untreated. It will be demonstrated that this day marks the usual limit of the illness as judged by the duration of symptoms and signs other than fever.

The greater length of pyrexia in patients with rash (figure 4) is justification for their separate consideration elsewhere.

Late Fever. A finding of conjectural significance was the occurrence of sporadic, low-grade temperature elevations during the convalescence of some patients. These transient "late fevers" followed the initial febrile phase of the acute infection by at least 48 hours, and were not associated with other evidences of relapse. The majority of such delayed fever reactions were manifested by only two or three recorded elevations of temperature. Late fever was present in one-quarter of the "untreated" patients, and one sixth of those treated by intermittent penicillin injections (penicillin I). It was uncommon in the group (penicillin II) treated with frequent injections of penicillin (only one-twelfth of patients).

Rantz and his associates [8] noted recrudescent fever unassociated with evidence of local pyogenic disease in 14 convalescent victims of streptococcal pharyngitis. In contrast to patients in the present series, these individuals usually suffered severe malaise. Electrocardiographic evidence of carditis and prolonged elevation of the erythrocyte sedimentation rate were noted in several of the patients in Rantz's study, leading him to the conclusion that late fever was a non-suppurative manifestation of the "post-streptococcic state" analogous to arthritis and carditis.

Duration of Local Symptoms. The complaints of "sore throat" and pain on deglutition were considered to be logical indices of the persistence of pharyngeal cellulitis. Other symptoms indicative of upper respiratory tract inflammation are nasal congestion, stiff neck, and otalgia. Patients were questioned with respect to the duration of such symptoms on the fourth day of hospitalization. The majority of patients, regardless of treatment, were free of complaints by the fourth day (table 2). It should be noted, however, that 17.2 per cent of patients receiving only symptomatic treatment experienced local symptoms after this time. Such symptoms were usually mild unless classed below as complications.

Duration of Systemic Symptoms. The term "systemic symptoms" includes all complaints not immediately referable to the upper respiratory tract, such as headache, malaise, chilliness and myalgia. Again, no important differences were noted in the duration of such symptoms in the three groups. There was a close parallelism between the duration of local and systemic complaints. The proportion of patients with systemic complaints after four days was very small, and approximately of the same extent in the three treatment groups. The apparent greater duration of symptoms in the

group treated with penicillin II is more probably related to the infrequency of chart notations than any failure of this regimen, because, as stated before, data relative to several members of this group were unconfirmed personally by the present investigators.

Duration of Physical Signs. The persistence of such signs as pharyngeal injection, edema, and exudate was noted on the fourth day of illness. Despite the early subsidence of local symptoms, approximately two-fifths of patients in both control and penicillin-treated groups had residual signs of pharyngeal infection on the fourth day. The average duration of such signs was about four days in the two groups subjected to careful observation (table 2).

Pyogenic Complications. Peritonsillar abscess was the commonest complication observed. Two "untreated" patients and two patients receiving intermittent penicillin (penicillin I) developed this condition. The group treated with frequent injections was notably free of pyogenic complications of the acute disease.

Two cases of acute purulent paranasal sinusitis diagnosed in the group receiving symptomatic treatment have been included as pyogenic complications, although sinusitis may be considered as an incidental part of the acute disease.

Purulent otitis media was not observed in this series.

Late Sequelae. All patients were followed for at least 21 days, and repeat throat cultures and blood for antistreptolysin titers were obtained at the end of that period. Most patients were assigned to the post for at least six months, during which time late effects of streptococcal infection should have become apparent, particularly because current policy dictated the hospitalization of all patients with fever.

Two patients developed obvious rheumatic fever, while another incurred arthralgia, prolonged fever, and elevation of the red blood cell sedimentation rate without developing the physical signs of redness or swelling of his joints. These three cases occurred in the group treated with large daily doses of penicillin (penicillin I). In the untreated group, one patient experienced prolonged fever (19 days), and another manifested microscopic hematuria on a single occasion, but showed no other evidences of nephritis.

The 29 patients treated with continuous penicillin dosage (penicillin II) apparently remained free of sequelae.

Relapses or Reinfections. Five patients experienced clinical relapses associated with the reappearance of beta hemolytic streptococci in predominant growth on pharyngeal culture. The reappearance of disease may have been true relapse caused by the original invaders, or may have represented "reinfection," or invasion by streptococci of another serologic type. Data on this question are not available. Two recrudescences, which occurred in the group treated with penicillin I, became evident on the third day after the cessation of therapy, whereas the three recurrences noted in the

group treated with penicillin II were delayed until the seventh, thirteenth, and twenty-first days after the discontinuation of treatment.

It may be significant that all patients who suffered recurrence of infection had been given antibacterial therapy. No relapses occurred in the control group. The statistical significance of this observation in the present series may be subject to challenge, but when it is correlated with the findings of others (Plummer et al.[9]; Rantz, Boisvert, and Spink [10]) it is strongly implied that relapse rates are higher in groups receiving penicillin treatment. In an early communication on penicillin therapy in hemolytic streptococcal pharyngitis, Plummer and his co-workers [9] noted clinical and bacteriological relapse 48 hours after cessation of therapy in four of nine patients treated

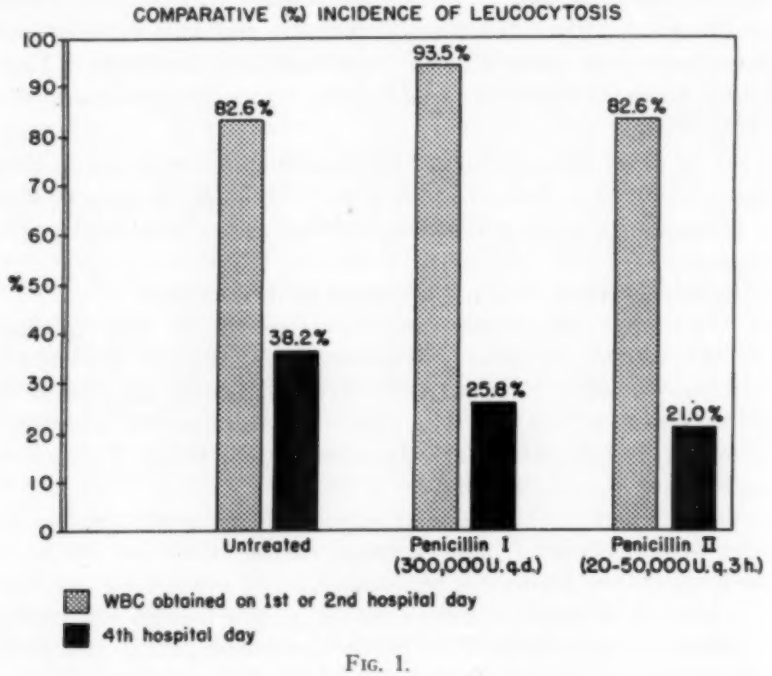


FIG. 1.

with penicillin for three or four day periods. Rantz et al.[10] described frequent bacteriological and clinical relapses in patients treated with either "short course(s)" (32 to 64 hrs.) or "long course(s)" (80 hrs.) of penicillin administered at four hourly intervals.

The immunological implications of these data will be discussed subsequently.

Duration of Leukocytosis. The infrequent determination of the total leukocyte counts makes this finding of little value in precise measurement of the duration of acute pharyngitis. However, comparison of the percentage incidence of leukocytosis on the initial and fourth day determinations adduces further evidence for the brevity of the disease process in all three groups

of patients (figure 1). Furthermore, significantly fewer penicillin-treated patients had abnormal total leukocyte counts on the fourth day than members of the "untreated" group.

Antistreptolysin Response. The antistreptolysin response of patients in the three treatment groups has been presented in detail elsewhere.[1] In summary, 84.3 per cent of untreated patients manifested a significant rise in the antistreptolysin titer; and in comparison, 63.8 per cent of those treated with large daily injections of penicillin (penicillin I), and only 13.8 per cent

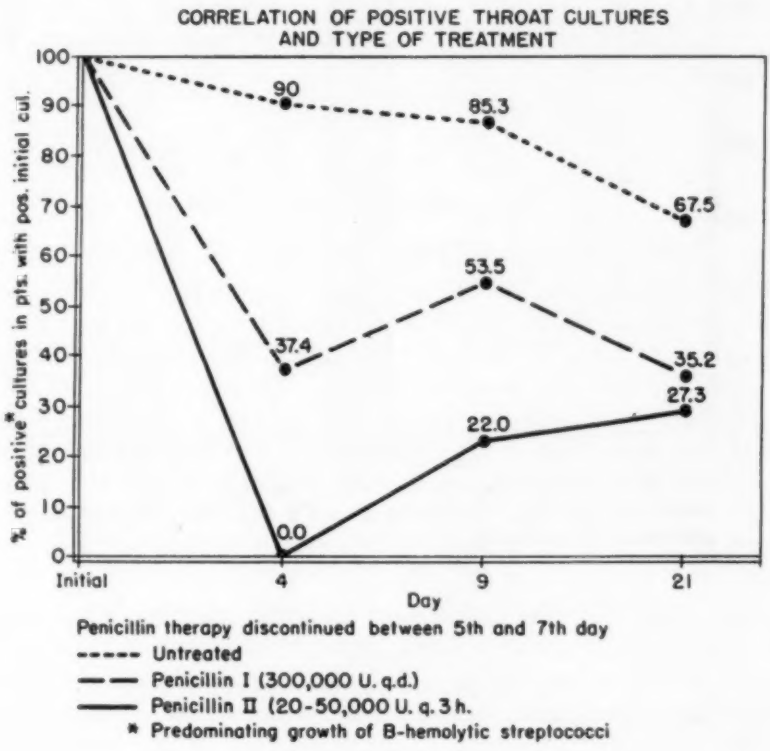
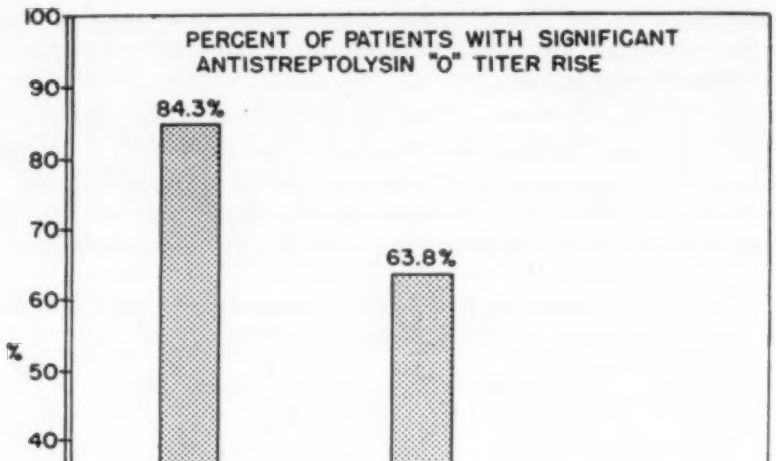


FIG. 2.

of patients who received small intermittent doses of penicillin (penicillin II) showed an antistreptolysin response (figure 3). The average amplitude of response paralleled the incidence of response, and was greatest in the untreated group, and least in patients treated with the schedule, penicillin II.

Duration of the Carrier State. Cultures of the posterior pharynx and tonsils were obtained on all patients at the time of admission, and were repeated thereafter on approximately the fourth, ninth, and twenty-first days following hospitalization. The results of this bacteriological survey are illustrated graphically in figure 2. It will be observed that bacteria disappeared gradually from the throats of patients in the control series, and that



Penicillin I = 300,000 units q d x 7, 47 patients
Penicillin II = 20,000-50,000 q. 3h. x 5 6 days (av.), 29 patients
Untreated = 51 patients

FIG. 3.

TABLE III

The Comparative Durations of Fever

Days	Untreated	Penicillin I	Penicillin II
1	9.3%	46.7%	8.7%
1½	16.3%	10.0%	30.4%
2	16.3%	33.4%	30.4%
2½	21.0%	3.3%	8.7%
3	11.6%	3.3%	17.4%
3½	7.0%	0	0
4	11.6%	0	4.4%
4½	2.3%	3.3%	0
5	2.3%	0	0
5½	0	0	0
6	2.3%	0	0
	100.0% (43)*	100.0% (30*)	100.0% (23*)

Penicillin I = 300,000 units q.d.
Penicillin II = 20–50,000 units q.3 h.
* Indicates number of patients.

more than two-thirds of these patients still carried streptococci in predominating growth after 21 days or more.

In contrast, a prompt decline in the incidence of positive throat cultures was evident on the fourth day in both penicillin-treated groups. In fact, cultures were uniformly negative in patients in whom continuously effective blood concentrations of penicillin had been maintained (penicillin II). The interesting direct relationship between the percentage of positive fourth day cultures and the incidence of antibody response will be discussed.

TABLE IV

Comparative Durations of Illness in Patients with and without Rash

Duration in Days	With Rash	Without Rash
Fever	2.9	1.7
Local symptoms	4.2	3.4
Systemic symptoms	4.5	3.4
Physical signs	4.1	4.3

All treated with penicillin I (300,000 units q.d.)

Cultures obtained on about the ninth day represented the first post-treatment cultures. The incidence of positive cultures continued to decline in patients who had received no antibacterial therapy, but increased in both penicillin-treated groups following the cessation of therapy.

By the twenty-first day, the incidence of positive cultures had continued to increase to a peak of over 27 per cent in patients treated with penicillin schedule II, but had declined in the control group and in the group treated with penicillin schedule I (large daily doses), to lower incidences than noted on previous cultures.

SCARLET FEVER

Eighteen patients had cutaneous eruptions of sufficient extent and duration to justify the diagnosis of scarlet fever. In nine cases the offending streptococcus was type 19, in three, it was type 23, and in six cases, typings were not obtained. Twenty-four illnesses in the total series were caused by type 19, whereas type 23 was responsible for 56.

The bulk of current opinion favors the concept that scarlet fever is merely streptococcal pharyngitis with rash (Rantz and Boisvert [2]). Certainly, there is no important epidemiological difference between the two diseases. In the absence of uniformity of opinion on this point, patients with rash will be considered separately for the purpose of comparison with other studies. As indicated before, no controls are available for the evaluation of treatment effects in this group.

One symptomatically-treated patient experienced 2.5 days of fever, was a carrier of streptococci on the twenty-first day, and developed an anti-streptolysin response.

Six patients were treated with penicillin schedule II. Fever averaged 2.5 days in duration, and patients suffered no complications, sequelae, or

relapses. None were carriers on the twenty-first day, and none manifested rises in antistreptolysin titer.

Eleven patients were treated with penicillin schedule I (300,000 units once daily). Data relative to these patients are summarized in table 3, and compared with data concerning patients without rash in the same treatment group. The small number of patients with rash mitigates against accurate comparison, but no striking difference in the durations of illness is evident. In this group no complications, but one relapse and one case of rheumatic fever occurred; about one-half showed antibody response, and four were carriers on the twenty-first day.

Discussion

The Acute Disease. Penicillin, whether given in continuous or intermittent dosage, did not significantly modify the symptomatology of hemolytic streptococcal pharyngitis, but did reduce the period of pyrexia and leukocytic reaction. The shorter mean duration of fever in penicillin-treated patients was not paralleled by shorter periods of throat pain or abnormal physical signs than were observed in symptomatically-treated patients.

The rapid elimination of most of the infecting organisms by penicillin probably obviates prolongation of the host defense reactions of pyrexia and leukocytosis. Subsidence of local pharyngeal inflammation is understandably slower. The early and frequent relapses noted when penicillin is discontinued after one to three days [9, 11, 12] are evidence that reduction of the number of streptococci in the throat and tonsils is not complete nor immediate. It is possible that sufficient bacteria remain to perpetuate the local pathological process, but are inaccessible to routine cultural procedures. Furthermore, the brevity of the acute disease tends to minimize differences of reaction within its usual three day span. This factor probably explains in part the failure of penicillin to shorten the duration of systemic symptoms.

Pyogenic Complications. Few pyogenic complications were observed in this study of 127 patients. As might be anticipated, four untreated patients suffered extension of the local pyogenic process, whereas none of the patients who received penicillin in conventional dosage (penicillin II) were so affected. Two of 47 patients who received 300,000 units once daily (penicillin I) developed peritonsillar abscesses. It is notable that elimination of streptococci was less rapid in this group than in patients treated with penicillin II. However, the total number of patients was less in the latter group so the differing incidence of complications in the penicillin treated groups may not be of significance. The value of penicillin in conventional dosage is well established. Hirsh and his associates, in a study of the treatment of scarlet fever, found that penicillin therapy resulted in a "decided reduction in the incidence of pyogenic complications" [12]; and a similar investigation by Hoyne and Brown [13] resulted in a similar conclusion. In patients who are not under constant surveillance, the use of penicillin in

streptococcal pharyngitis appears justified, if only from the standpoint of the prevention of pyogenic extension of the disease.

Late Sequelae. No late sequelae of streptococcal infection occurred in patients in whom effective blood concentrations of penicillin had been continuously maintained for four to seven days (i.e.: penicillin II). In this group of patients, elimination of streptococci was more rapid, and antibody response (antistreptolysin) was minimal in incidence and degree (figure 2).

Three cases of rheumatic fever followed treatment with intermittent penicillin therapy (penicillin I). In this group over 60 per cent of patients showed an antibody response, and a higher percentage of patients maintained hemolytic streptococci in their throats than in the former group. It is of interest that all three cases developed rises in antistreptolysin titer, either prior to or coincident with the appearance of rheumatism. Two patients on symptomatic therapy developed late sequelae. Both manifested rises in antistreptolysin titer.

The occurrence of high antistreptolysin titers in patients with acute rheumatic fever has been frequently observed.[14] This phenomenon was originally described by Todd[15] and adduced as evidence that rheumatic fever was a sequel to streptococcal infection. The correlation between antistreptolysin response and rheumatic activity was subsequently noted by Coburn and Pauli[16] in the study of an outbreak of streptococcal pharyngitis in a home for rheumatic children. They reported that 14 rheumatic subjects out of 16 exposed developed acute rheumatic exacerbations accompanied by rises in antistreptolysin titers, following infection. Weinstein and Tsao's recent study of scarlet fever patients[4] disclosed that all subsequent cases of rheumatic fever occurred in patients who developed rises in antistreptolysin titer.

The conception of rheumatic fever as an allergic reaction to the hemolytic streptococcus has led to a search for a sensitizing antibody. In a recent paper Rantz and Randall[17] described an unidentified "anti-x antibody" which occurred more frequently in patients developing arthritis than in uncomplicated streptococcal pharyngitis.

There is no evidence that antistreptolysin is directly related to the rheumatic allergic state. It is, however, an easily measurable antibody demonstrable in 78 to 90 per cent[18] of streptococcal infections. Evidence has been cited that the incidence of this antibody response is diminished by penicillin therapy.[1, 4] One may speculate that treatment which prevents the formation of one streptococcal antibody may suppress the production of others, including the sensitizing antibody of rheumatic fever. Interference with antibody formation by penicillin is most logically related to the early removal of the antigenic streptococcus (figure 2). Dowling and Hirsh remarked that penicillin quickly reduced the "toxicity" in scarlet fever, without neutralization of the erythrogenic toxin.[19] These investigators believe that the apparent antitoxic effect of penicillin results indirectly from the rapid elimination of the organisms producing toxin. The present authors noted persistence of a positive Dick test in two patients with scarlet fever treated

with penicillin. Pursuant to this reasoning, it is of interest that two rheumatic subjects treated immediately with penicillin for acute streptococcal infections developed no increases in antistreptolysin titers, and no recrudescences of rheumatic fever (Goerner, Massell, and Jones [20]). Controlled studies of large rheumatic populations are needed for the evaluation of these preliminary observations.

Relapses or Reinfections. The five relapses noted in this group of 127 patients occurred in penicillin-treated patients. The frequent relapses observed in penicillin-treated patients in other series has been commented upon. In three patients in the present series (all treated with continuous penicillin therapy) it was established that prior to the second illness no antistreptolysin response had occurred. In two of these patients who received no antibacterial therapy during the recurrence, significant antistreptolysin responses then occurred.

It is suggested that the coincidence of diminished antibody formation and greater relapse rates in penicillin-treated patients may be related to the early reduction in streptococci (without their complete extirpation) thus preventing the development of natural immunity.

The Carrier State. Penicillin treatment greatly lessened the incidence of positive cultures observed at the twenty-first day, whether administered in daily or three-hourly injections. The epidemiological implication of this observation is obvious. It must be pointed out, however, that in a group of scarlet fever patients followed carefully by Rubenstein and Foley [21] a period of "cultural latency" occurred in sulfonamide treated patients which apparently had *no significant effect on the incidence of late secondary cases.* In approximately half these cases it was noted that the original streptococcus reappeared in the cultures after an interval of one to five weeks. In the present study, the incidence of positive cultures in patients treated symptomatically or with penicillin schedule I showed progressive decline, in contrast to the progressively increasing positive cultures noted in patients who had received frequent injections of penicillin. One is tempted to relate this phenomenon to the diminished antibody formation in this latter group.

Summary

1. The natural history and results of treatment of 127 cases of streptococcal pharyngitis and scarlet fever have been presented and discussed.

2. The comparative effects of symptomatic treatment and therapy with two penicillin regimens were studied with reference to the course of the acute disease, the incidence of pyogenic complications, late sequelae, relapses, the carrier state, and antistreptolysin formation.

Conclusions

1. Penicillin therapy does not significantly modify the symptomatology of streptococcal pharyngitis, but shortens the mean duration of fever and leukocytosis.

2. Penicillin administered by frequent injections in conventional dosage (20,000 to 50,000 units) probably reduces the incidence of pyogenic complications.

3. Penicillin therapy reduces the incidence and degree of antibody response as measured by the antistreptolysin titer. This interference with the antibody mechanism is less marked in patients treated with large single daily doses of penicillin.

4. The suppression of antistreptolysin response by penicillin is probably mediated by early reduction of the number of streptococci in the pharynx.

5. Penicillin therapy reduces the incidence of pharyngeal carriers observed at the end of three weeks.

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CASE REPORTS

RENAL DWARFISM WITH HYPERPARATHYROIDISM IN A CASE OF CONGENITAL FAMILIAL MALFORMATION OF THE KIDNEYS *

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The clinical picture of dwarfism in children, with or without rickets, in combination with pathological states of the kidneys, has been observed and reported fairly frequently in the last decades, after it had been recognized as a clinical entity by Fletcher (1911).[13] Descriptions and discussions of this condition are given in a number of monographs and textbooks on children's diseases,[30, 32] bone diseases,[40] kidney disorders,[41] as well as in textbooks on pathology and clinical physiology. However, the condition is a rare one, and some of its principal features, especially with regard to its etiology, are not yet fully clarified.

In short, renal dwarfism consists of stunted growth, retardation of sexual development, but in most cases normal mental development, combined with symptoms of renal impairment, such as polyuria, isosthenuria, hyposthenuria, presence of albumin and pus cells in the urine, and progressive uremia. Other related features are increasing weakness, anemia, dry and coarse skin with yellow pigmentation and multiple brown spots. Hypertension and changes in the eye fundus are usually absent. In the last decade a number of cases have been reported in which a marked hypertrophy of the parathyroid glands was found at autopsy; in some cases (Shelling and Remsen [38]) the hyperactivity of these glands could be demonstrated during life by the method of Hamilton and Schwartz.

The retardation of growth is often, but not always, combined with skeletal deformities, not unlike those of rickets, which are referred to by the former designation of the condition as "renal rickets." Other names of this disease are "osteonephropathy" and "renal osteodystrophy," stressing the connection between the renal and the osseous changes, while the names "renal osteitis fibrosis cystica" and "renal hyperparathyroidism with osteoporosis fibrosis cystica" are designed to express a definite opinion on the cause of the frequently present changes in the bone structure and their connection with the parathyroid glands.

The kidney lesion which is found in these cases is either of the inflammatory type (glomerulonephritis or interstitial nephritis) with progressive destruction of the functional tissue, or it is of the type of renal malformation, with or without obstruction of the urinary passages, and in many cases with superimposed ascending infection of the renal tissue. This latter type has attracted in the last few years the special interest of urologists to the syndrome of renal dwarfism (Howard [19]; Charnock [4]; Harrison [17]; Hayward [18]; Hughes and Gislason [20]), as these

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cases seem to be amenable to prevention and therapy by early recognition of the underlying disorder and by surgical correction of the obstruction. According to the literature, the cases of renal dwarfism combined with the congenital type of renal disorders seem to prevail among the total number of cases (Ellis and Evans [10]; Hamperl and Wallis [16]; Anderson [2]).

According to the opinion of most of the observers, especially as reported in the Anglo-American and Scandinavian literature, there is no doubt as to the causal relationship between the bone disorder and the disease of the kidneys. These authors base their views on the assumption that the skeletal changes usually appear at a much later date than the kidney lesions, at a time, indeed, when impaired kidney function has already caused a severe disturbance in the mineral metabolism of the body and its fluids. This time relation granted, it still remains to be defined what is the exact character of the causal relationship, as well as the rôle of other abnormalities, especially the hyperplasia of the parathyroid glands, in the chain of events.

It is well known (Mandl [26]; Albright,[1] and many others) that primary hyperparathyroidism, caused by a tumor of one or more of the parathyroid glands, may lead to bone changes (osteitis fibrosa, osteoporosis), and to metastatic calcinosis in the kidneys, with impairment of the renal function, and it is not unlikely that some of the cases described as "renal rickets" were really cases of primary hyperparathyroidism with secondary skeletal changes and renal damage.

On the other hand it has been shown (Pappenheimer and Wilens [31]) that experimental reduction of renal tissue in rats and longstanding nephritis in man, even in adults, leads to decalcification of bones and to hypertrophy of the parathyroid glands. This mechanism, initiated by the insufficiency of the kidneys, is claimed as effective in the genesis of renal dwarfism by practically all those observers who maintain a causal relationship between the kidney disorder and the skeletal changes. In addition to this mechanism it may happen that the secondarily hypertrophied parathyroids act like primary tumors of these glands and lead to calcification and additional damage in the kidneys.

The precise mechanism by which the renal insufficiency exerts its influence on the bones and the parathyroid glands has been the subject of many discussions and of experimental investigations. Some authors (Parsons [33]; Mitchell [28]; Drake, Albright and Castleman [9]) regard the retention of phosphate by the damaged kidneys as the decisive chemical factor, and it has been shown experimentally (Pierre and co-workers [34]) that hyperphosphatemia causes increase in weight of the parathyroid glands. Other observers (Albright, Drake and Sulkowitch [2]; Ham [15]; Kaijser [22]) believe that the hypocalcemia caused by the increased excretion of calcium-phosphate through the intestines is the main factor, while by many (Jaffe, Bodansky and Chandler [21]; Mach and Rutishauser [25]; Graham and Oakley [14]; Snapper [40]; Tomenius [41]) the chronic acidosis of renal insufficiency is held responsible. The retardation of growth is explained by some authors (Danis and Rossen [6]; Smyth and Goldman [39]; McConney [27]) by the "antigrowth factor of the parathyroids" of Thompson.[36, 42]

This interpretation of the causal interrelationship between the kidney changes and the bone deformities, well founded as it seems to be in a great many cases, does not fit all the reported instances of renal dwarfism. Especially it leaves unexplained those numerous cases in which the skeletal changes consist only in stunted growth, without marked decalcification or rickets-like deformities, and

those in which the above mentioned time relation between the appearance of the kidney lesions and the bone changes cannot be demonstrated. Those cases clearly demand a different explanation which may be found in the direction indicated especially by French and German authors. Nobécourt and Kaplan (1934) [30] designate as unauthorized the conclusion "that the statural hypotrophy and the dwarfism, associated with affections of the kidneys and urinary passages, are caused by the latter" ("rien n'autorise à conclure . . . que l'hypothropie staturale et le nanisme, associés à des affections du rein ou des voies urinaires, en soient la conséquence"). Debré and co-workers (1937) [7] clearly express the same view, but they accept the "phosphatemia-theory" of Parsons and Mitchell for some cases which actually present primary renal insufficiency and secondary rickets-like bone changes. The explanation offered by these authors as well as by the German observers of this condition (Loeschke [24]; Hamperl and Wallis [16]) is that the dwarfism or infantilism and the malformations of the urinary tract are parallel, but not interdependent expressions of congenital disturbances. Loeschke [24] cites as proof for this theory a case of dwarfism combined with severe malformations of the urinary passages, but without any signs of diminished ability of the excretory functions of the kidney. Further proof for this explanation may be found in the frequent occurrence of other congenital malformations or functional disorders in cases of renal dwarfism, for instance in the combination with hypochloremia and glycosuria (Fanconi [11]; de Toni [8]) or with abnormalities in the cystine metabolism (Lignac [23]). All these disturbances may be regarded, according to Rule and Grollman,[37] as belonging to one clinical syndrome.

As to the question of a common, possibly endocrine factor for all these abnormalities, most of the French and German authors as well as some English and American authors (Chown [5]; Anderson [3]; Price and Davie [35]; Moehlig [29]) point to the pituitary gland (and the diencephalic region) as the probable seat of the primary congenital disturbance.

The following case is reported as an example of renal dwarfism with hyperparathyroidism, but without severe bone changes, in which the renal disorder as well as the retarded growth was observed from earliest infanthood, both of them probably resulting from a congenital disturbance. Moreover, this case seems to be of particular interest as the kidney disorder was not only congenital but also familial, and of a kind which apparently has not yet been described in the literature.

Case Report

The patient, S. S., a girl 13 years of age, was sent to the outpatient department by a school nurse who, during a routine examination, had found albumin in her urine. Because of the visible retardation of growth, a connection of this with some underlying kidney disorder was suspected and the girl was admitted to the hospital for a thorough examination.

The girl's mother, M. S., was a patient of the same department seven and four years previously. She was suffering from "congenital anomaly of the kidneys, pyelitis and chronic nephritis," and died in January 1940 from "uremia and septicemia." It was noted that she was of small stature, but otherwise she showed no malformations. Her age at the time of death was 35. Figure 2 shows the pyelogram which was taken from this patient. The methylene blue excretion of the right side was delayed and very poor.

One elder sister of our patient, L. S., was examined in 1942. The girl was at that time 18 years old, but gave the impression of an underdeveloped girl of about 15 years. According to information received from her father, she had always been somewhat delicate and underweight, but showed no other abnormalities. In 1942 her urine contained traces of albumin and many pus cells. The same findings were present in April 1944. At this time her blood pressure was 120 mm. Hg systolic and 60 mm. diastolic. The chemical analysis of her blood showed 17.5 mg. per cent urea, 3.5 mg. per cent uric acid, 11 mg. per cent calcium, 4.5 mg. per cent phosphorus and 11 units

FIG. 1. The patient (right), S. S., at the age of 14½ years, together with a girl of the same age.

phosphatase. The kidneys were examined by methylene blue excretion and retrograde pyelography. The right kidney showed retarded dye excretion. The pyelogram (figure 3) showed a hypoplastic kidney on the right side, resembling the malformation found in her mother, M. S., and her sister, S. S.

History: Our patient had had abnormal urinary findings since early infanthood, and had also shown marked retardation of growth observable in the first year of her life. At the age of one and one-half years she was smaller than another girl of the same family who was then only six months old. She continued, however, to grow and her mental development was quite normal. She attended school according to her age.

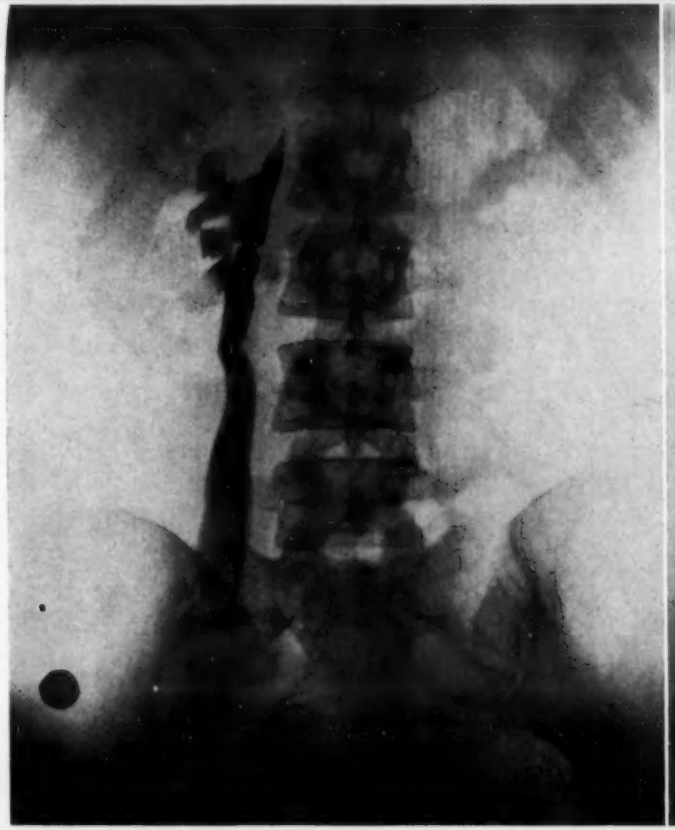

FIG. 2. M. S., mother of the patient, at the age of 32. Retrograde pyelography of the right kidney: Dilatation of the pelvis and of the calices, the upper calix elongated, in straight line with the ureter. The other calices are short and blunt. The ureter appears as a dilated inelastic tube. (The left kidney and ureter were normal by excretory urogram.)

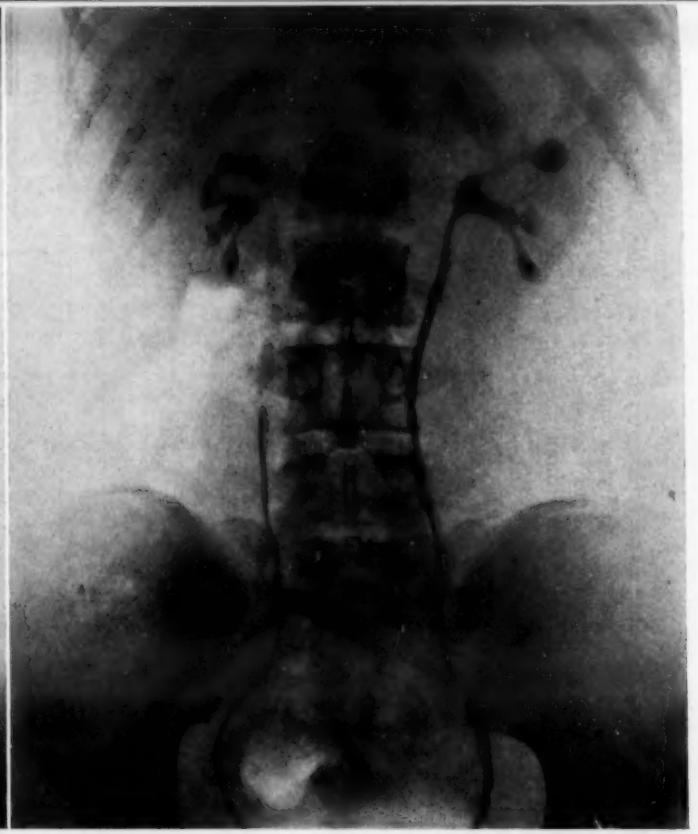

FIG. 3. L. S., elder sister of patient, aged 18 years. Retrograde pyelogram. The right kidney has a small thin amount of renal parenchyma, the pelvis is small, the calices are short and blunt, with little renal tissue between them. Note compensatory hypertrophy of the left kidney, with large amounts of renal tissue.

In April 1940, at the age of 10 years, she was examined by a urologist (Dr. W. Nissel). His findings revealed an underdeveloped girl, but general examination was normal. The urine contained many pus cells. Cystoscopic examination showed normal bladder and ureteral openings. Methylene blue, after intravenous injection, appeared on the left side after five minutes, on the right side after seven minutes. Ureteral catheters passed on both sides without difficulties. Ureteral urine contained pus cells, right more than left. Intravenous pyelography was attempted but did not visualize the kidneys. For retrograde pyelography see figure 4.

During the following years her health chart contained repeated observations on general weakness, low specific gravity of the urine, with findings of albumin and pus cells. In November 1940, at the age of 10 years, her height was 117 cm., and her weight 19.3 kilograms, the normal figures for this age being 128 cm. and 26 kg. respectively. In October 1942, about one year before her first hospitalization, her blood urea was 85 mg. per cent.

TABLE I

Blood Findings during the First Stage (Chronic, Latent Renal Impairment)

Date	Urea mg. %	Uric Acid mg. %	Sugar mg. %	Calcium mg. %	Phosphorus mg. %	Phosphatase Units	CO_2 Vol. %	Total Prot. gr. %	R.B.C. Millions	Hgb. %	W.B.C.
Oct. 27, 1942	85								4.03	72	
Dec. 26, 1943	175	6.05							3.8	65	10,200
Dec. 27, 1943	196										
Dec. 30, 1943				10.3	5.1	5.9					
Jan. 6, 1944				10.5	5.6	4.4					
Feb. 8, 1944	122.5						30.9				
May 29, 1944	91	6.35	78								
Aug. 7, 1944	77	5.8							4.0		6,000
Sept. 16, 1944	147	6.2		9.8	6.1			7.45	3.09	60	5,100

On admission to hospital, in December of 1943, the physical examination showed a somewhat pale and undernourished, but otherwise normal girl, of an apparent age of eight or nine years, her real age being 13½ years. Her height was 131 cm., her weight 22 kg., instead of about 145 cm. and 36 kg. According to the classification of Wetzel [43] she belonged to group B_4 ("poor"), with development of 55 units, corresponding to a normal child of seven and one-half years. She showed no secondary sex characteristics and had not begun to menstruate. Her skin was dry, pale, and showed a yellowish tinge. The hair was also dry and lacked the normal luster. The girl was mentally alert; her intelligence and her interests were those of her actual age. She did not complain of anything and the physical examination did not reveal any abnormal findings. Her blood pressure was 110 to 130 mm. Hg systolic and 80 to 100 mm. diastolic. The eye fundi were without pathological changes. Dental examination showed calcification, dentition, and development of teeth to be normal and in accordance with her age. Basal metabolism was + 5 per cent.

Laboratory examinations: Red blood cells 3.8 millions, hemoglobin 65 per cent, white blood cells 10,200 per cu. mm., with a normal differential count. Urinalysis:

specific gravity 1.004 to 1.007, albumin ++++. In the sediment there were many pus cells and some red cells present. Urine culture revealed *Bacillus coli.*

At that time her blood urea was 175 to 196 mg. per cent. For other chemical findings in the blood see table 1.

Roentgenographic examination of heart and lungs was normal. Skeleton and skull were without visible decalcification or deformities. The kidneys could not be visualized by intravenous pyelography; retrograde filling showed the same picture as in figure 4.

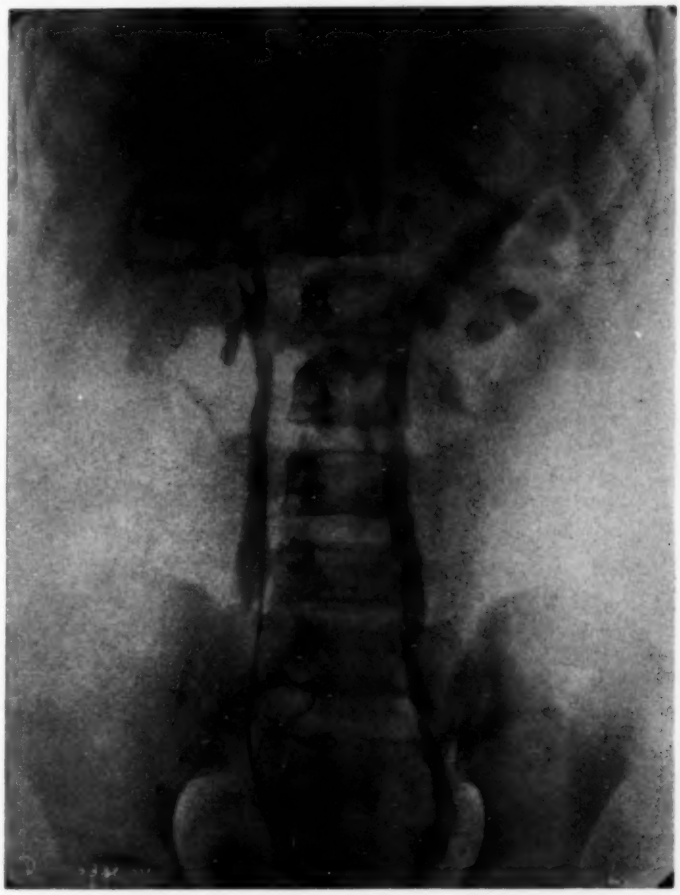

FIG. 4. S. S., the patient, at the age of 10 years. Retrograde pyelography. Right kidney: Small pelvis with rudimentary deformed calices. Left kidney: Slightly dilated pelvis and calices. Overdistention of both ureters. (The plain roentgen-ray picture showed a very small right kidney in contrast to a large kidney shadow on the left side.)

On the basis of the history and the clinical and laboratory findings a diagnosis was made of renal dwarfism, represented by retardation of growth and development, in connection with a congenital abnormality and chronic inflammation of both kidneys.

During the following period the patient was seen and examined from time to time. For about one year her condition was essentially unchanged as far as the kidney function and general symptoms were concerned, but, on the other hand, there was from this time on a complete arrest of her development and the retardation, relative

TABLE II

Blood Findings during the Terminal State (Severe, Manifest Renal Insufficiency, with Hyperphosphatemia and Acidosis)

Date	Urea mg. %	Uric Acid mg. %	Sugar mg. %	Calcium mg. %	Phosphorus mg. %	Phosphatase Units	CO_2 Vol. %	Total Protein gr. %	Albumin gr. %	Globulin gr. %		R.B.C. Millions	Hgb. %	W.B.C.
Feb. 8, 1945	315	6.6	110		8.9		17.6							
Feb. 16, 1945	438	7.0					14.7				Creatinin +++			
Feb. 19, 1945	455			10.4	12.1	10.2		8.55	6.1	2.45				
Feb. 23, 1945												2.88		8,600
Feb. 26, 1945	385				13.8	10.3	42.4	8.86	5.8	3.06				
March 5, 1945	437	7.5		9.3	13.6		38.2							
March 12, 1945	458	8.5		12.8	10.0		32.0							
March 15, 1945	445						37.6							
March 21, 1945	500						30.9	8.15					40	
March 27, 1945												1.22		18,600

to her age, became more prominent. Figure 1 shows the patient together with another patient of the same age.

In February 1945 she was again hospitalized. At that time she had begun to feel rather weak, suffered from headaches and vomited frequently. Her skin was dry, scaly and more yellow than previously, with numerous brown spots, especially on the face and on the forearms. The laboratory examinations revealed a severe degree of uremia, hyperphosphatemia, acidosis and anemia (table 2). The uremic state became more and more pronounced, she lost her appetite entirely, and vomited nearly all food. Bleeding from the nose and the intestinal tract appeared, and the girl died finally from uremia and anemia.

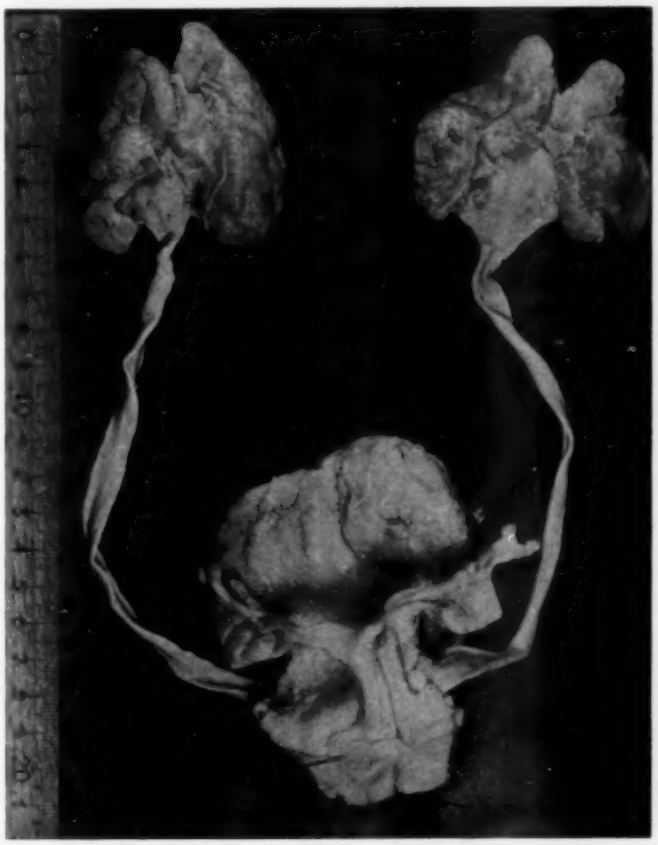

FIG. 5. Kidneys and pelvic organs, posterior aspect. The contraction of kidneys, hydropelvis and hydroureters are on view. Note the infantile configuration of the uterus.

Necropsy was performed two hours after death by Dr. E. Freund. Anatomical diagnosis: Hydropelvis and hydroureter, bilateral, of unknown origin. Marked atrophy of kidneys. Chronic interstitial nephritis. Focal suppurative (ascending?) nephritis.

Secondary hypertrophy of two parathyroid glands.

Foci of suppurative bronchopneumonia of the right lung.

Terminal verrucous thromboendocarditis of the mitral valve.

Osteoporosis of petrous bones.

Hypoplastic uterus and adnexes.

The body was that of a young female measuring 135 cm. in length. No secondary sex characteristics were present. The skin was pale. There were brown pigmented spots scattered over face, trunk and extremities. Emaciation was marked. There was no edema and no palpable lymph nodes.

The more important findings were as follows. Urinary tract (figure 5): The right kidney weighed 25 gm., and measured 5 by 2 by 2 cm. The organ was firm in

FIG. 6. Larynx with thyroid and parathyroid glands, posterior aspect (moderately enlarged). Two parathyroids are on view, the right one measuring in nature 20 by 8 by 5 mm.

texture. The thin fibrous capsule was firmly adherent to the cortical surface. Cut surface was yellowish-brown throughout. Cortico-medullary border was not clearly defined. The renal pelvis and calices were considerably dilated and the renal papillae were entirely flattened. Corresponding with the dilated calices the parenchyma was markedly atrophic; it measured in some areas but 2 mm. in thickness and in no place more than 20 mm. The right ureter was extremely dilated, measuring in its upper third about 10 mm. in diameter. Mucosa of pelvis and ureters was without defects. The left kidney weighed 30 gm., and measured 6 by 3 by 2 cm.; it was

similar in aspect to right kidney. The urinary bladder was moderately distended with urine. The mucosa was pale, with scattered verruca-like tiny elevations of reddish-brown color. Openings of ureters were without lesions.

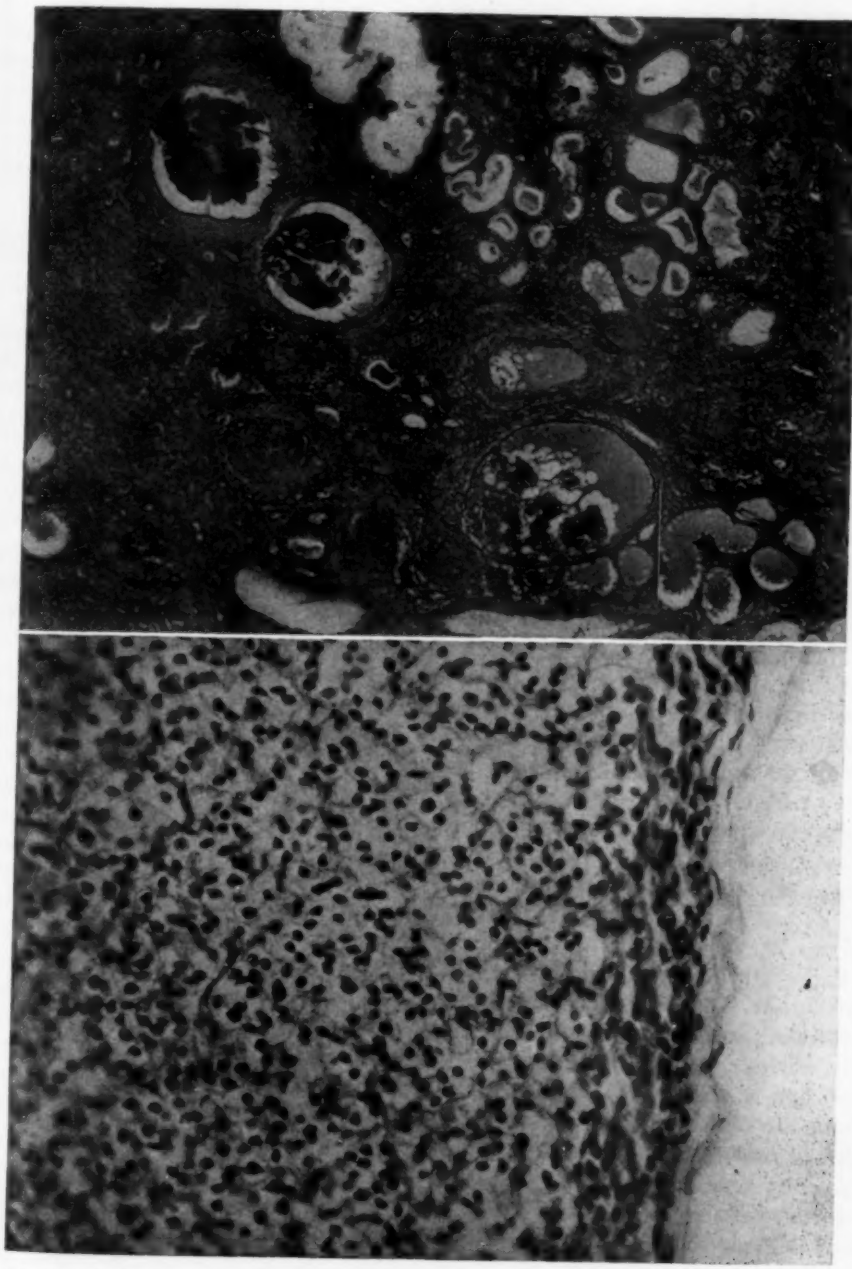

FIG. 7. (*Above.*) Section of the kidney (see text).
FIG. 8. (*Below.*) Section of the enlarged parathyroid gland (see text).

Parathyroid glands: In the place corresponding to the lower parathyroids, two round bodies were found, each one being about the size of a small bean (figure 6). Cut surface revealed yellowish-brown tissue, containing a dark reddish center.

Costochondral junctions were grossly without changes. Epiphyseal regions of long bones were not thickened. Calvarium could be sawed with ease.

Histological examination (Dr. H. Ungar). Kidneys: Glomeruli were irregularly distributed and diminished in number. In some instances they were larger than normal, with dilated spaces of Bowman, containing pale coagulated material (figure 7). Capillaries had normal content of nuclei.

There were also scattered glomeruli which were partially or entirely hyalinized. The degree of hyalinization varied in different areas, and was more marked in areas of extreme atrophy of the parenchyma.

Extensive atrophy of tubules was observed in the vicinity of all glomeruli. In irregular distribution there were groups of hypertrophic tubules, lined by clear cubical epithelium. The increased fibrotic interstitial tissue contained infiltrations of lymphocytes and scattered polymorphonuclear leukocytes and plasma cells. In one area a small abscess was found, surrounded by tubules distended with abundant cellular debris and leukocytes. The arterioles were without pathological changes; the medium-sized arteries showed marked thickening of all layers. There was only negligible increase of elastic fibers. The parathyroids were uniformly built of clear chief-cells. No cells of other types or fat-cells were found (figure 8).

Discussion

In its essential features our case fits well into the known picture of renal dwarfism and belongs to the group A(1) of Rule and Grollman (primary renal disease with well recognized anatomical changes). It presented stunted growth (without manifestations of rickets), infantilism, and severe impairment of the renal function, leading to uremia and death. Moreover, the autopsy revealed hypertrophy of the parathyroid glands of the type found in secondary hyperparathyroidism. The kidney lesions were those which are found in the majority of cases of renal dwarfism, i.e., bilateral congenital dilatation of the pelvis and the ureters with atrophy of the renal parenchyma and interstitial nephritis. Besides, there were signs of superimposed focal suppurative nephritis. Also, the age of the patient at the time of manifestation of severe renal symptoms and of death corresponds to that usually attained in such cases. The absence of fundus changes and of pronounced degrees of hypertension, as well as the mental alertness, are likewise common in this disorder.

There are, however, some points which seem worth stressing, as they may contribute to the solution of the question of the connection between the disturbed renal function and the skeletal changes.

In our case, the retardation of growth was noted as early as in the first year of life, and was already marked at the age of one and one-half years. It is highly improbable that already at this early date the kidney function was disturbed to such a degree as to be the cause of the impaired growth. On the other hand, the kidney lesion belonged to the congenital type of this disorder and was likewise present at the time of birth. It seems, therefore, justified to assume that in our case there existed a congenital malformation of the kidneys, together with a congenital tendency to dwarfism which became manifest as early as the first months of life.

A further proof for this assumption is to be found in the family history. The mother and the sister were definitely below normal height, and both these members of her family showed the same malformation of the right kidney as our patient had on both sides.

The roentgenological appearance of the right kidney is strikingly similar in all three cases, and this fact in itself deserves special stress, as it seems to be the only case on record in which three members of one family had the same congenital malformation of this type.

We may say, accordingly, that this case of renal dwarfism was caused primarily by a congenitally present kidney malformation and a hereditary tendency to stunted growth, both of these based on a familial trait, but most pronounced and leading to the fully developed picture of renal dwarfism only in our case. As to a common root of these disorders in a pituitary or diencephalic factor, we can make no definite statements, as other abnormalities usually connected with such a disturbance were lacking, but it may be mentioned that the lack of secondary sex characteristics and the hypoplasia of the uterus and its adnexes point in this direction.

For our case we can, therefore, dispense with any theory of chemical or functional interrelationship between the kidney disorder and the dwarfism, in order to explain the clinical and laboratory findings which were present until two to three months before her death. Up to this time blood urea and uric acid were elevated without pronounced hypocalcemia, hyperphosphatemia or severe acidosis, and it was only about two months before her death that the inorganic phosphorus in the blood began sharply to rise and to reach 13.8 mg. per cent, and the acidotic state to become severe and to depress the alkali reserve to 14.7 vol. per cent CO_2. It may be repeated here that the microscopic findings were those of an active interstitial nephritis and foci of suppuration within the renal parenchyma, and these alterations more than the primary congenital malformation caused the extreme reduction of normal tissue and the final breakdown of the kidney function, with the severe alterations in the blood chemistry, during the last two to three months (table 2).

As to the hypertrophy of the parathyroid glands which was found at autopsy, it may well be assumed that it resulted from the chemical changes brought about by the renal insufficiency during the last two to three months, a time interval which seems to be sufficient, according to the experiments of Pierre, de Boissezon and Lombard,[34] to bring about a marked increase in the weight of these glands. This hypertrophy, however, was apparently not present long enough to produce more than the slight osteoporosis which was observed in the petrous bones.

This interpretation of the course of events in our case is primarily in accordance with the theory of renal dwarfism as a syndrome of parallel, noninterdependent, congenital disturbances, affecting the general growth and development and the urinary tract. However, the hypertrophy of the parathyroid glands and the slight osteoporosis fit also into the other theory, maintaining a causal relationship between the kidney insufficiency and the skeletal deformities. Our case actually needs both of the described theories for a satisfactory explanation, the former for the manifestations during the greater part of the patient's life and the latter for the last few months after the kidney insufficiency had become extreme and had led to severe acidosis and phosphatemia. It seems possible that in other cases, too, there may be two stages in the development of the syndrome:

in the first, latent kidney damage and stunted growth, both of them congenital, are present; in the second manifest renal insufficiency, hyperparathyroidism and structural changes of the bones are observed. A careful correlation of all available data, especially regarding the time of onset of the various clinical symptoms and of the blood findings, is necessary in order to find out, in questionable cases, the presence of one, or possibly both of the above described mechanisms. In some cases, as in ours, examination of other members of the family may prove helpful, in order to establish proof of the congenital character of both conditions.

Summary

The syndrome of "renal dwarfism" may be explained by two different theories. The first, prevalent in the English and American literature, assumes a causal dependence of the bone changes upon the kidney disorder; the second, advanced chiefly by French and German authors, describes both groups of changes as parallel, non-interdependent, congenital malformations.

A case is described of renal dwarfism in a girl of 14 years, without bone deformities, but with hypertrophy of the parathyroid glands and slight osteoporosis. The congenital nature of the kidney disorder, the retardation of growth since early infancy, and the presence of corresponding kidney disorders and subnormal stature in two other female members of the same family seem to justify the explanation of this case on the basis of the theory of "multiple congenital malformations." The supervening secondary hypertrophy of the parathyroid glands and the slight osteoporosis are explained, on the basis of the other theory, as a result of the renal insufficiency.

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THIOURACIL IN ACUTE THYROIDITIS *

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ACUTE thyroiditis has been treated in a few instances with thiouracil [1] and the results have been very encouraging. The following two cases are reported to show the striking response to this drug after a thorough and adequate course of penicillin and sulfadiazine had failed to relieve any of the signs or symptoms.

CASE REPORTS

Case 1. A female, married, age 38, was seen on September 1, 1945, with a history of frequent chills and fever occurring, especially at night, during the preceding 10 weeks. She complained of an aching feeling in the head, pain in the neck in the thyroid region which spread into the jaws and upward into the neck, palpitation, distress in the abdomen not related to any special food-taking, loose stools, anorexia, weakness, and loss of about 20 pounds in weight during the interval of the past 10 weeks. She claimed that her health was good prior to the onset of this trouble and that her menstrual history was normal. Her past history revealed a gall-bladder operation and an appendectomy nine years previously. She has three children, the youngest six months of age.

Examination showed an acutely ill individual with a temperature of 99.5° and an enlarged, smooth, hard, tender thyroid, especially the lower portion of the lobes on both sides. Her throat and mouth were negative, as were the heart and lungs. Her blood pressure was 120 mm. Hg systolic and 82 mm. diastolic. Her abdomen was negative and also her pelvic organs. There was no evidence of trouble in the extremities.

Her laboratory report showed a 52 per cent hemoglobin, 10,700 white cell count, and a 3,550,000 red cell count with a sedimentation rate of 102 mm. in an hour. The hematocrit was 26.25 per cent MCV 74, MCH 25, and MCHC 36, revealing a microcytic anemia. The common agglutination tests and blood culture were negative, and the Wassermann test was negative. The blood sugar reading was 88 mg. per cent, and the non-protein nitrogen was 38 mg. per cent. The urine examination was negative. The basal metabolism was plus 6 per cent. Roentgen-ray examination of the chest was negative.

Sulfadiazine in doses of 1 gm. every four hours for 10 days and again for six days after an interval of one week gave no signs of improvement. Penicillin in doses of 30,000 units every three hours intramuscularly for six days also failed to show any changes in the signs and symptoms.

Thiouracil (Deracil) † in doses of 0.2 gm. three times daily was started on Sep-

* Received for publication March 12, 1947.
† Deracil used in case 1 was supplied by Lederle Laboratories.

tember 18, 1945. Her temperature became normal in 48 hours and remained so from that time on, with an immediate improvement in all her symptoms. The gland remained swollen and hard, but this too gradually subsided, so that on February 15, 1946, no evidence of swelling could be found.

Thiouracil was given in full dosage of 0.2 gm. three times daily for one week; then the same dose twice daily for two weeks; and then 0.1 gm. daily for three months.

Six weeks after discontinuing the drug there was a slight recurrence of the acute symptoms with slight swelling of the lower portion of both lobes. Thiouracil in doses of 0.2 gm. three times daily for one week and twice daily for another week caused all signs and symptoms to disappear, and there has been no evidence of recurrence since that time. She has gained weight, her blood picture has become normal, she is working and apparently has no residual effects from this inflammatory condition.

Case 2. A male, age 32, was seen on September 10, 1946, with a complaint of chills and fever and sweats at night extending over a period of three weeks, during which time he lost weight, became weak, was unable to eat, and had pains in his neck extending up toward the ears. He had headaches and had pains in his arms and legs, especially at night. His past history showed no evidences of this condition prior to the onset above noted. While in the South Pacific he had been ill for one month with jaundice and had, for several months prior to his discharge from the Army, complained of pain in his ears, the cause of which could not be determined. His family history was negative.

Examination showed an acutely ill individual with a temperature of 99.6°, a pulse of 90, and a hard, tender swelling of the lower poles of both lobes of the thyroid, a negative chest, and a blood pressure of 120/82. His liver and spleen were not enlarged, and there was no tenderness in the abdomen. His extremities were negative. Laboratory examination showed 80 per cent hemoglobin, 14,700 white blood cells, and 4,370,000 red blood cells, with a sedimentation rate of 33 mm. in one hour. The common agglutination tests, Wassermann test, and blood cultures were negative. Basal metabolic rate was plus 9 per cent. His blood sugar was 114 mg. per cent and the non-protein nitrogen 32 mg. per cent. The blood smears were negative for malaria, and his icterus index was 11.3. His urine examination was negative. He was hospitalized on September 10 and placed on 30,000 units of penicillin every three hours for six days with no material change in his condition or his complaints. His temperature during this time rose to spikes of 101°, and his pulse varied from 72 to 104. On September 16 he was given 0.2 gm. of thiouracil three times a day, and this was continued for seven days, when the dose was reduced to 0.2 gm. twice daily and continued as such until November 1.

The results of this treatment were a normal temperature 24 hours after beginning administration of the drug, with no subsequent elevation, and a gradual diminution of all symptoms and findings started immediately His white blood count was 6,500 five days after beginning use of the drug. On November 1, there was no longer any evidence of swelling of the gland, no chills or fever or pain, and he has remained perfectly well since that time. He has regained his normal weight, has been working at a strenuous occupation, and on several instances has been examined with no evidence of any residual findings.

Comment

The pharmacological reason for this improvement is difficult to understand, but the response in both cases was so prompt and similar that it could not be a coincidence. The therapeutic results indicate that the infection probably, in some way, is linked up with the process of the production or liberation of thyroxin.

The failure of both penicillin and sulfadiazine to improve the first case and the lack of effect from penicillin in the second case are especially noted.

Probably the swelling of the gland in the first case would have disappeared in a shorter time if the dosage of 0.2 gm. twice daily had been continued a few weeks longer, and the recurrence of the symptoms thereby might have been avoided.

Conclusions

Two cases of acute thyroiditis responded rapidly to treatment with thiouracil.

These two cases were resistant to treatment with other methods, including penicillin and sulfadiazine.

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ANTERIOR PITUITARY INSUFFICIENCY (PANHYPOPITUITARISM—SIMMONDS' DISEASE), PITUITARY MYXEDEMA AND CONGESTIVE HEART FAILURE (MYXEDEMA HEART); REPORT OF CASE AND FINDINGS AT NECROPSY *

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Anterior pituitary insufficiency (panhypopituitarism) may result from any pathologic process that destroys the anterior lobe. The most common lesion is the chromophobe tumor. Less frequently, other nonfunctioning neoplastic lesions, granulomas, chronic infections, atrophy, necrosis, hemorrhage, infarction or miscellaneous vascular disturbances account for pituitary failure. The terms "Simmonds' disease" and "Simmonds' cachexia" [1] have been applied, often indiscriminately, either to pituitary necrosis that occurs postpartum or to cachectic patients having, or thought to have, anterior pituitary insufficiency for other reasons. Clinically, the symptom complex that characterizes postpartum pituitary necrosis is essentially the same as that which occurs in conjunction with any other destructive lesion of the anterior lobe of comparable magnitude. Sheehan [2] has pointed out that cachexia, as a symptom of postpartum pituitary necrosis, is the exception rather than the rule. The same dictum applies for that matter to any other form of anterior pituitary insufficiency. Even when cachexia occurs, as it undoubtedly does in some instances, there is considerable reason to suspect that it may have very little or nothing to do with the anterior pituitary insufficiency per se but that it results from the same factors that cause cachexia in other patients; namely, an inadequate caloric intake or vomiting or both. Regardless of its interpretation, the fact remains that in a group of patients having severe anterior pituitary insufficiency of comparable degree, some are fat, some are nor-

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mal in weight, others are lean and a few are cachectic. The hypotheses that can be, and have been, offered to explain this paradox leave much to be desired and for present purposes, can be disregarded without comment.

The emphasis that has been placed on cachexia as a sign of postpartum pituitary necrosis has had unfortunate diagnostic consequences. In many instances, because of the presence of cachexia, anorexia nervosa has been diagnosed erroneously as Simmonds' disease and conversely cases of frank postpartum pituitary necrosis have been overlooked because the patient was not cachectic. There is, therefore, little excuse for retaining the terms "Simmonds' disease" or "Simmonds' cachexia." Clarity of thought would be greatly facilitated if the gross pathologic and physiologic status of the patient were expressed more specifically, as for example "postpartum pituitary necrosis with anterior pituitary insufficiency, with (or without) cachexia" or "chromophobe tumor of the pituitary body with anterior pituitary insufficiency and pituitary myxedema with (or without) cachexia" and so forth.

The signs and symptoms of severe anterior pituitary insufficiency are to a large extent, but probably not entirely, the result of varying degrees of secondary gonadal, adrenal and thyroid insufficiency. Generally they are sufficiently distinctive to enable one to differentiate it from other endocrinopathies. Often the diagnosis is evident on inspection by the characteristic waxy pallor, feebly growing beard and sparse cutaneous, pubic and axillary hair. The skin is soft and fine. In women the uterus is small and the vaginal mucosa is hypoplastic; in men the testes are soft or atrophic. When the disease antedates puberty, sexual development ceases. Skeletal growth likewise usually stops, but if it should continue, as it does occasionally, the extremities become unduly long and the habitus of the patient resembles that of the eunuch. Such cases, however, are the exception rather than the rule and the consequence of this fact is that a eunuchoid habitus is usually indicative of a primary gonadal disorder rather than anterior pituitary insufficiency. As has been mentioned, the patient may be fat, thin or of normal weight but the distribution of fat may be feminine in character. Frequently the patient complains of weakness. There is a history of decreased or absent potentia, anaphrodisia or amenorrhea without hot flushes. Laboratory examinations show a low basal metabolic rate, a flat glucose tolerance curve, normal blood or varying degrees of anemia, a "positive water test" such as occurs in Addison's disease and decreased or absent urinary 17-ketosteroids and gonadotropins. Depending on the nature of the pathologic process and the amount of residual functioning pituitary tissue that has escaped destruction, some of these symptoms and signs may be absent. For example, in cases of chromophobe tumor, amenorrhea may be for years the only symptom of the disease. Even in cases of severe anterior pituitary insufficiency the function of gonads, thyroid and adrenal glands may not be disturbed equally in any particular patient. For example, in a few cases adrenal cortical insufficiency is so prominent that the clinical picture presented by the patient greatly resembles that of Addison's disease, whereas in others adrenal cortical function is apparently so slightly affected that its insufficiency cannot be demonstrated with certainty. To a lesser extent the same is true of thyroid function. On the other hand, gonadal function is relatively easily upset by anterior pituitary failure and consequently in practically every instance evidence of gonadal failure can be obtained.

Ordinarily the clinical picture just described bears little resemblance to pri-

mary myxedema and, conversely, the ordinary case of spontaneous or postoperative myxedema does not simulate anterior pituitary insufficiency. Occasionally, however, during the course of anterior pituitary insufficiency, the patient acquires secondary myxedema, presumably because of inadequate production of thyrotropic hormone by the anterior pituitary body. When this occurs, the skin becomes thick, dry, coarse and scaly and nonpitting edema of the hands, face and lower extremities appears. This secondary myxedema resembles ordinary myxedema in every major or minor respect. In fact, it is myxedema but a myxedema superimposed on the original clinical picture of anterior pituitary insufficiency. Means, Hertz and Lerman [3] suggested that the term "pituitary myxedema" be applied to this condition so as to distinguish it from ordinary or primary myxedema. Although one might question the merits of this particular term, there are good reasons for making the distinction. All of the symptoms of primary myxedema respond to treatment with desiccated thyroid and the patient is "cured" as long as he continues to take the medication. Pituitary myxedema likewise responds to administration of desiccated thyroid but the patient remains ill because of the other disorders attending anterior pituitary insufficiency, which naturally are not corrected by desiccated thyroid. Furthermore, some patients who have pituitary myxedema may become very ill and die when first treated with desiccated thyroid, possibly because of the precipitation of acute adrenal cortical insufficiency.

If the patient has the signs and symptoms of an expanding intrasellar tumor such as bitemporal headache, bitemporal hemianopsia or other characteristic changes in the perimetric fields and characteristic roentgenologic changes in the sella turcica, it is relatively easy to make a correct diagnosis. If the patient is a woman and her illness began after a difficult delivery, complicated by shock hemorrhage or both, one can suspect that she has had "pituitary apoplexy" and that her illness is the consequence of the resulting pituitary necrosis. On the other hand, if there is no evidence of a pituitary tumor and if the condition did not develop post partum, the myxedema may dominate the clinical picture to such an extent that the signs and symptoms of the primary pituitary insufficiency are overshadowed and consequently not detected. In such cases recognition of pituitary myxedema may be very difficult.

Primary myxedema may lead to characteristic and almost pathognomonic changes in the status of the heart. Zondek,[4] Assmann,[5] Meissner,[6] and Fahr [7] were among the first to demonstrate this fact. Subsequently their observations have been confirmed repeatedly by others. The "myxedema heart," or, as Means [8] prefers, "the heart in myxedema," is characterized by flabby musculature and enlargement of all four chambers, probably because of dilatation. The minute volume output is reduced. In the electrocardiogram, the complexes are of low amplitude, the T-waves, particularly in Leads I and II, are flattened or inverted and other less significant abnormalities may be present.* In our experience, as well as that of Means,[9] gross congestive heart failure rarely occurs, probably because, as Means pointed out, with "reduction in the heart's capacity for work there goes a parallel reduction in the amount it is called upon to perform." On the other hand, cases reported by Fahr, by Mussio Fournier,[10] and by La Due [11] leave little room for doubt that in certain instances primary myx-

* Mussio Fournier and his associates have recently published an excellent monograph on the cardiovascular apparatus in thyroid insufficiency.

edema may be accompanied by all signs and symptoms of severe congestive heart failure and that the myxedema is largely, if not entirely, responsible for the occurrence of these signs and symptoms.

In this connection the case of La Due is of considerable importance. The patient was a woman, aged 55 years. She had myxedema and the signs and symptoms of congestive heart failure. Arteriosclerotic damage of the myocardium was conspicuously lacking and the coronary arteries were perfectly normal except for one small atheromatous nodule, which reduced the caliber of one of the small branches of the left descending coronary artery to a half. La Due also pointed out the interesting similarity of the myocardial lesions to those found in beriberi heart. In addition, he reviewed the history of another patient who had myxedematous heart, who did not respond to intensive thiamine and vitamin B complex therapy for 33 days. There was, however, a rather rapid response to treatment with desiccated thyroid within eight days and, after 25 days of treatment, the electrocardiogram was essentially normal.

La Due's observations seem to establish the fact that the cardiac pathologic physiologic state of patients having myxedema results from thyroid deficiency rather than thiamine deficiency. They do not preclude the possibility that utilization of available thiamine by the myocardium might be impaired by inadequate thyroid function.

The foregoing remarks regarding the heart apply to cases of primary myxedema. That they may be applicable to cases of pituitary myxedema is suggested by the case reported by Darley, Gordon and Neubuerger [12] and by the observations made on the patient the report of whose case follows. In the former case, issues are somewhat confused by the presence of "an old rheumatic mitral valvulitis." In our case the valves and the coronary arteries were normal.

Case Report

The patient was a white man, aged 47 years, who came to the Mayo Clinic February 16, 1943, because of weakness, anorexia and dyspnea on exertion. On the whole his health had been good until the onset of his present illness, which he thought dated back to 1939 or 1940. In 1931 he had sustained an injury to the left eye from a glancing dull object. There was no loss of consciousness or headache but the left eye became swollen, red and painful for several days without any known residual. In 1936, following a cold in the head, his left eye became swollen to twice its normal size, reddened and painful. There was transient impairment of the sight. Following treatment the swelling receded entirely, but slight strabismus and ptosis persisted.

At no time was the patient known to have hypertension. In 1939 his physician commented on the redness of his cheeks and thought that he might have high blood pressure. However, the blood pressure was found to be normal (130 mm. of mercury, systolic). There was no history of rheumatic fever.

The onset of the patient's present illness was insidious. Other than a gradual decrease in libido for the preceding three years, he had not noticed any change until February, 1942, when he became progressively weaker. His appetite declined and he lost weight. The weakness was most pronounced toward the end of the day and it became so severe that he had to be helped into his car after office hours. At the onset of his illness he weighed 169 pounds (76.7 kg.) but five months later he weighed 129 pounds (58.5 kg.).

In the latter part of May, 1942, the patient became so weak that he could hardly sit at his desk. Associated with the weakness was mild exertional dyspnea. By this

time he had complete absence of libido and potentia. He consulted his physician, who prescribed rest in bed and general therapeutic measures. As improvement did not result, he entered a hospital on June 15, 1942. There he was found to have a low basal metabolic rate, low blood pressure, and mild anemia. A presumptive diagnosis of Addison's disease was made. Within three weeks he improved rapidly following the administration of thiamine chloride and injections of suprarenal cortical extract. His strength and appetite returned and his weight increased to 174 pounds (78.9 kg.). He was permitted to leave the hospital July 6, 1942. His family physician was advised to administer daily injections of suprarenal cortical extract (5 c.c.) for two weeks and then bi-weekly injections for three weeks.

Progress continued until August, 1942, when he stopped taking the injections of suprarenal extract because of nervousness. In November, 1942, he had a return of weakness and anorexia, whereupon he took three injections of suprarenal cortical extract and again his condition improved. This time the improvement did not persist and soon his weakness and dyspnea returned. In January, 1943, he contracted a severe head cold and became very ill. This illness was characterized by weakness, anorexia, dyspnea, orthopnea with nocturnal paroxysms, enlargement of the abdomen (ascites?), and cough productive of frothy sputum. He had no noticeable edema of the ankles. In addition he had mild diarrhea of soft watery stools, two to three times daily. On questioning, he stated that he had always had rather sparse beard and body hair and had noticed no decrease; however, the texture of the hair of the scalp had become silky. He had also noticed that the skin had taken on a yellowish hue and had become dry. He had noticed no abnormal sensitivity to cold.

Examination. The temperature, pulse and respirations were essentially normal. The blood pressure in millimeters of mercury was 94 systolic, 68 diastolic. The height was 177 cm., and the weight 76.7 kg. There was no evidence of loss of weight; on the contrary he was well developed and well nourished. His general appearance immediately suggested the diagnosis of myxedema to the physician who first examined him. He looked older than his stated age. There was fine wrinkling of the skin, which was thin, dry, scaly and pale yellow. The hair was very soft and silky in texture. The beard was very scant and there was no axillary hair. Less than normal pubic hair was present and its contour was feminine in type.

The head was not remarkable except for the left eye. There was incomplete paresis of the left third and fourth cranial nerves. The left pupil was almost fixed and there was marked limitation of upward and downward movements with only slight limitation of inward rotation. There was weakness of the left orbicularis oculi muscles. The visual fields were normal. Nothing of consequence was seen in the ocular fundi.

There was no glandular enlargement. No thyroid tissue was palpable in the neck.

There were bilateral hydrothorax and pulmonary congestion. The heart was markedly enlarged both to the right and to the left. There were numerous extrasystoles and the sounds were very distant. No apical impulse was seen or felt.

The abdomen was enlarged. There was ascites and the liver was tender and palpable 2 inches (5 cm.) below the costal margin. The spleen was not felt. The genitalia appeared normal. The testicles and prostate felt normal in size and consistency. The recovery phase of the ankle jerks was slow and typical of those seen in cases of myxedema.

Laboratory findings are recorded in table 1.

Diagnosis. That the patient had severe anterior pituitary insufficiency (posttraumatic?) and congestive heart failure was easily recognized. It was also evident that the hypopituitarism was associated with secondary gonadal and thyroid insufficiency. By inference it seemed likely that adrenal cortical function was also impaired and the likelihood was strengthened by the advent of such unfavorable clinical symptoms as hiccup, nausea, abdominal pain and decreasing blood pressure when the

TABLE I

Laboratory Findings

Urinalysis		
Specific gravity	1.024	
Reaction	Acid	
Albumin	Grade 1*	
Sugar	0	
Hematologic findings		
Hemoglobin	10.8 gm. per 100 c.c. blood	
Erythrocytes	4,010,000 per cu. mm. blood	
Leukocytes	5,400 per cu. mm. blood	
Comment on blood smears	Increased erythrocyte regeneration with mild hypochromasia	
Blood chemical findings		
Urea	34 mg. per 100 c.c. blood	
Sugar	94 mg. per 100 c.c. blood	
Chloride (as NaCl)	561 mg. per 100 c.c. plasma	
Sodium	308 mg. per 100 c.c. plasma	
Potassium	20.6 mg. per 100 c.c. plasma	
Protein	6 5 gm. per 100 c.c. serum	
Cholesterol	157 mg. per 100 c.c. plasma	
Carbon dioxide	42.8 vol. per cent	
Bilirubin, direct	0	
indirect	0.75 mg. per 100 c.c. serum	
Miscellaneous		
Water test†		
Procedure I: $\frac{\text{greatest vol. day urine}}{\text{vol. of night urine}}$	0.14	
Procedure II: A (urea-chloride index)	12	
Glucose tolerance test	Blood sugar, mg. per 100 c.c.	Urine sugar
Fasting	81	0
½ hour	119	0
2 hours	144	0
3 hours	140	0
Basal metabolic rate	−23 per cent	
Prolan (gonadotropic)	Less than 10 rat units per liter	
Total 17-ketosteroids	0.4 mg. per 24 hours	
Liver function	Dye retention, grade 2*	
Venous pressure	21.4 mm.	
Circulation time (arm to tongue)	15 sec.	
(arm to lung)	6 sec.	
Flocculation test for syphilis	Negative	
Roentgenograms		
Head	Calcified petroclinoid ligament. Rather marked calcification left internal carotid artery	
Thorax	Cardiac enlargement. Some exaggeration hilar marks on both sides, probably due to passive congestion. Extensive thickening of pleura and possibly fluid on right. Some compression basal portion right lung	
Electrocardiogram	Rate 100; sinus tachycardia with ventricular premature contractions; notched QRS I and III, slurred II, very low amplitude QRS I, II, III, diphasic I and III, slight left axis deviation (PR = 0.20 second). IV-R: Positive T. Low amplitude QRS Cr −2. Low amplitude. Positive T. Slightly elevated ST segment	

* On the basis of 1 to 4, in which 1 represents the mildest and 4 the most severe condition.
† Procedure of Robinson, Power and Kepler.

intake of sodium chloride was restricted as a therapeutic measure to restore cardiac compensation. Furthermore, these symptoms were relieved by intramuscular administration of 10.0 c.c. of cortical extract.

The cause of the heart failure was the most difficult diagnostic problem. Here five possibilities had to be considered.

1. Preëxisting hypertensive heart disease. This possibility seemed to be excluded fairly well by the clinical history, the electrocardiogram and the shape of the roentgenologic silhouette of the heart.

2. Pericarditis with massive effusion. This possibility seemed unlikely because of the absence of the usual etiologic factors responsible for this condition. In addition the physical signs which often accompany massive pericardial effusion were absent and the venous blood pressure was not increased.

3. Beriberi heart. This possibility was suggested by the shape of the heart shadow, the electrocardiogram and the low venous pressure. As a possibility it was

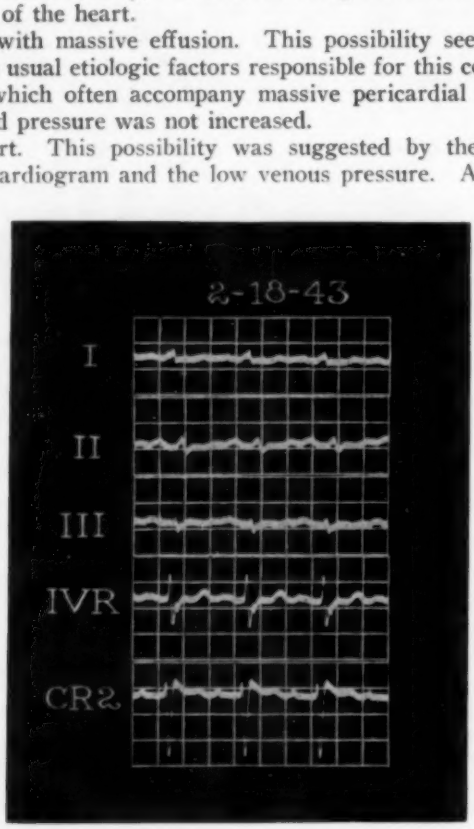

FIG. 1. Electrocardiogram of the patient.

never very satisfying. None of the other physical signs or symptoms of beriberi were present, there was no history of dietary inadequacy and the intravenous administration of 40 mg. of thiamine daily did not produce either subjective or objective improvement.

4. Hemochromatosis was considered very seriously in the diagnosis. It could account for the appearance of pituitary insufficiency, the enlarged liver and the congestive heart failure. The patient was only slightly pigmented but in cases of hemochromatosis dense pigmentation need not be present. This diagnostic possibility was abandoned when biopsy of the skin failed to show characteristic deposits of iron.

5. "Myxedema heart." This possibility had much to recommend it. The low venous pressure, the pattern of the electrocardiogram (figure 1) and the shape of the enlarged heart were consistent, the patient clinically appeared to have myxedema and the basal metabolic rate was low (— 23 per cent) even though he had congestive heart

failure. Nevertheless, in spite of this evidence, we were reluctant to make an unqualified diagnosis of this for several reasons. The degree of myxedema was mild when compared with the severity of the heart failure. Furthermore, primary myxedema is rarely accompanied by nocturnal dyspnea and severe, rapidly progressive heart failure and whether or not myxedema secondary to hypopituitarism could ever lead to congestive heart failure was certainly a question without answer in the literature. After weighing the pros and cons we finally concluded that a diagnosis of "myxedema heart" was the most likely of the various possibilities which we had considered.

Treatment and Course. While the patient was being examined in the hospital, his heart began to fail rapidly and relief of the distressing symptoms attending the congestive heart failure required first attention. It was hoped that this could be accomplished by nonspecific measures and that subsequently specific treatment for the adrenal cortical and thyroid insufficiency could be instituted.

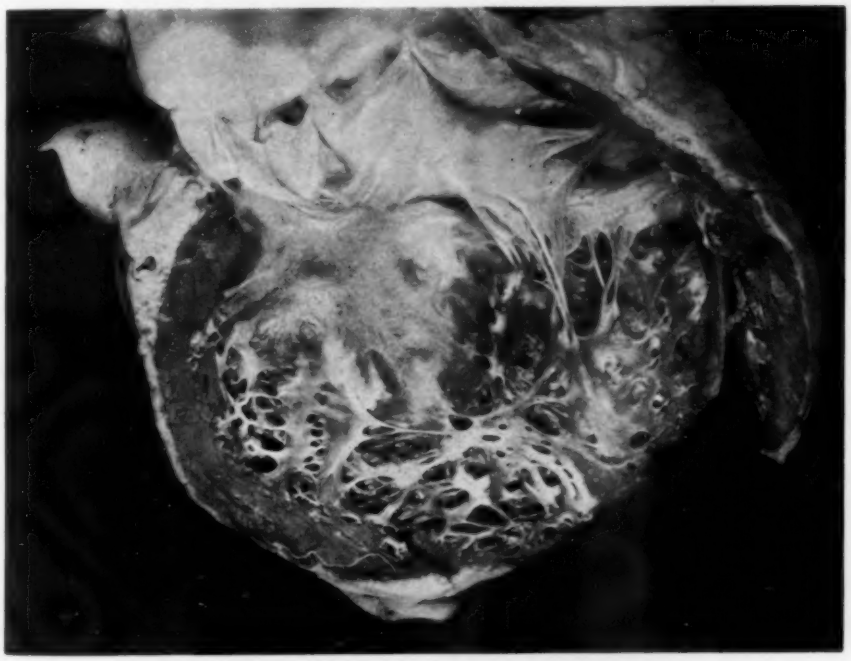

FIG. 2. Dilatation of left ventricle. Weight: 507 gm.

The treatment employed did not work out satisfactorily. As mentioned elsewhere, restriction of sodium chloride precipitated symptoms suggesting adrenal cortical insufficiency. These symptoms responded to the administration of 10.0 c.c. of adrenal cortical extract and the unrestricted use of table salt. Simultaneously, however, the patient became more dyspneic and edematous. Solutions of hypertonic glucose and aminophylline gave some relief, but the patient remained critically ill. One cubic centimeter of salyrgan was then given intravenously. Diuresis was prompt and copious and the patient improved subjectively and objectively. However, improvement was transient. There developed marked dyspnea and an irregular tachycardia suggesting paroxysmal auricular fibrillation. He was placed at once in an

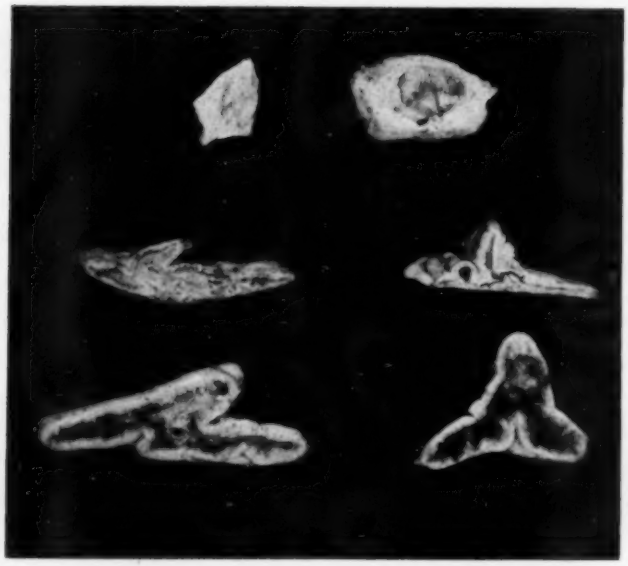

FIG. 3. Atrophy of pituitary body, above on left. Normal pituitary body for comparison, upper right. Atrophy of adrenal glands (middle) compared with normal adrenal glands below.

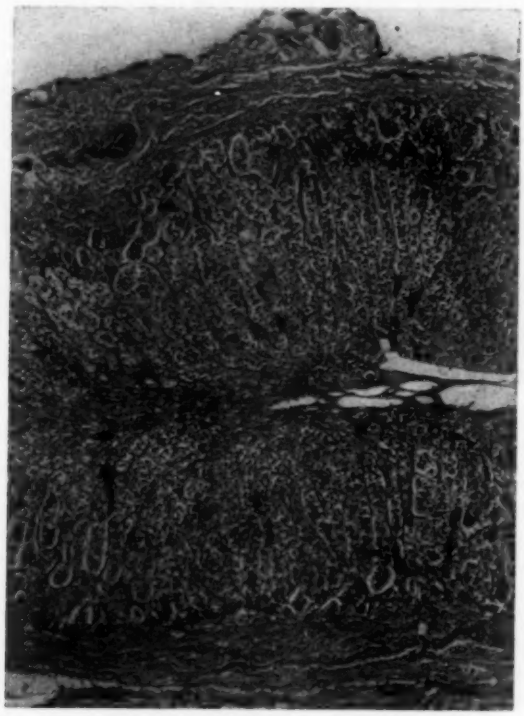

FIG. 4. Atrophy of adrenal cortex (× 55).

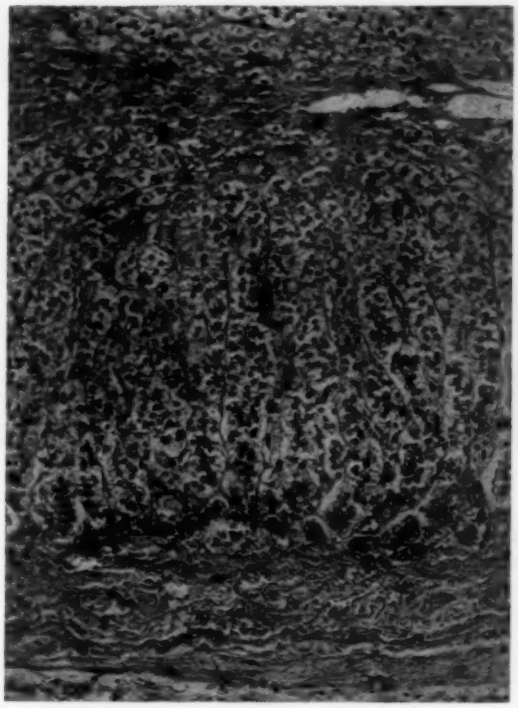

FIG. 5. High-power view of adrenal cortex. Medulla not shown (× 115).

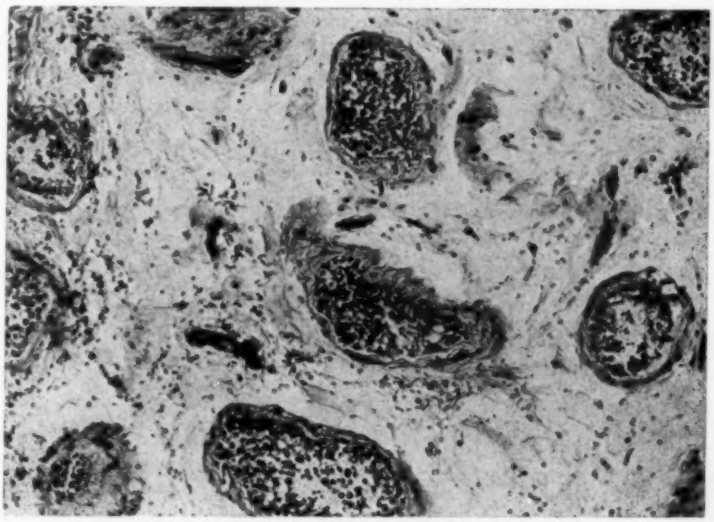

FIG. 6. Atrophy of testis (× 85).

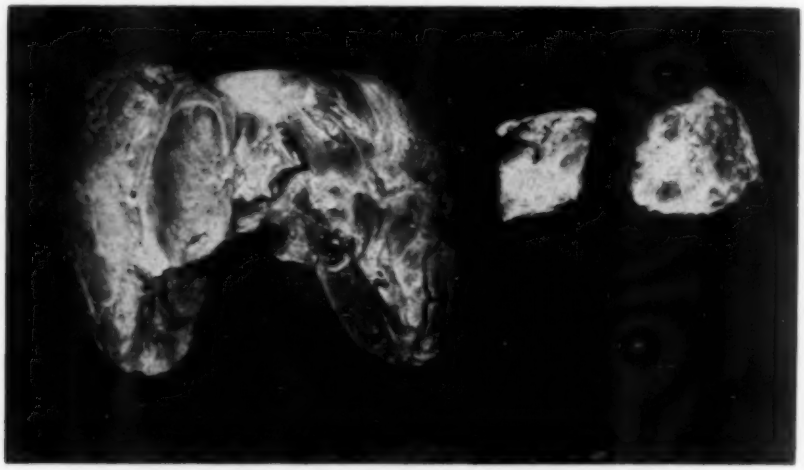

FIG. 7. Atrophy of thyroid (right). Normal thyroid gland for comparison (left).

oxygen tent and was given 6 c.c. of cedilanid intravenously. Cardiac rate and rhythm became normal and the patient felt better. Four hours later, he was given another 6 c.c. of cedilanid intravenously. Shortly thereafter, he vomited and while doing so he died, 13 days after admission to the hospital.

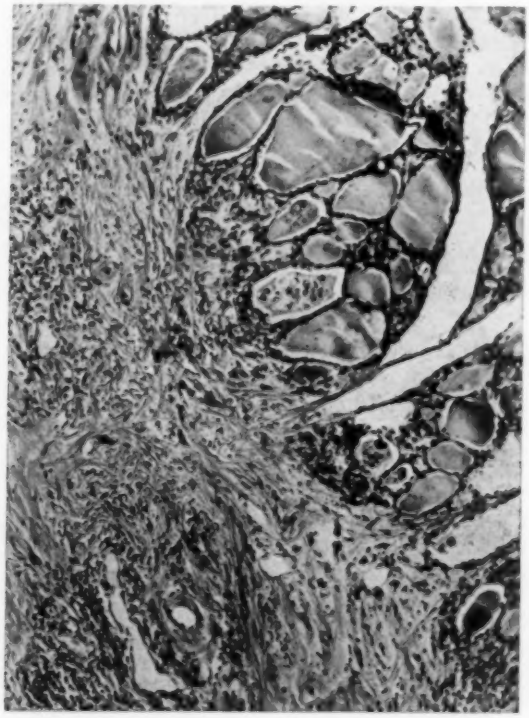

FIG. 8. Atrophy of thyroid with fibrosis and lymphocytic infiltration (×85).

Necropsy Findings. The body measured 177 cm. in length and weighed approximately 180 pounds (81.6 kg.). There was no emaciation. The parchment-like skin was tinged with yellow. The hair on the thorax and the pubic region was fine and scanty.

Bilateral hydrothorax was present (right 1,000 c.c., left 200 c.c.) associated with hydropericardium (75 c.c.) and ascites (2,000 c.c.). No thymic tissue was found. The heart (figure 2) weighed 507 gm. as compared with a normal weight of 320 gm. computed on the basis of body weight and sex. The hypertrophy was most marked in the left ventricle. Both ventricles were greatly dilated. The myocardium showed interstitial fibrosis with vacuolar degeneration of some muscle fibers. There was no arteriosclerosis of the coronary vessels. The lungs showed a moderate degree of chronic passive congestion and small focal regions of organized pneumonia. Passive congestion was noted in the spleen.

FIG. 9. Cross section of pituitary, marked atrophy (× 8).

The pancreas was atrophic and there was interstitial fibrosis with slight fatty replacement of the acinar elements. The islands of Langerhans appeared normal.

The liver showed the typical picture of chronic passive congestion with early central necrosis associated with atrophy (1,398 gm.; normal 1,800 gm.).

The gastrointestinal tract was normal.

The two adrenal glands (figure 3) weighed only 5 gm. The medulla showed a relative increase as compared with the cortex. The cortical cells (figures 4 and 5) contained an abundance of lipoid and appeared to be histologically normal except for a marked decrease in thickness of the cortex due to a diminished number of cortical cells in the zona fasciculata. The zona glomerulosa was prominent. A few microscopic cortical adenomas were present.

The kidneys were normal except for a calcified cortical adenoma with psammoma bodies.

The prostate was normal in size and shape. Chronic interstitial prostatitis, grade 1 (on the basis of 1 to 4, in which 1 represents the mildest and 4 the most severe condition), was present.

The testicles (figure 6) were moderately atrophic. The spermatogenic tubules were small and showed marked decrease in spermatogenesis. The interstitial connective tissue was increased. The tubules were surrounded by a dense ring of hyaline connective tissue. There was a paucity of interstitial cells; occasional cells were seen and they showed degenerative changes.

FIG. 10. Atrophy and fibrosis of the anterior pituitary body. Lymphocytes in connective tissue (× 85).

The thyroid (figures 7 and 8) was atrophic and fibrous. It weighed 5 gm. and was of normal contour. The acini was small with normal-appearing colloid. There was a slight increase in lymphocytes present. In some regions a large percentage of acini had been compressed by increased fibrous connective tissue.

The sella turcica appeared normal. The pituitary body (figures 3 and 9) was flattened and atrophic. It measured 9 by 6 by 2 mm. The stalk was prominent. On inspection with a hand lens, the normal divisions of the pituitary were absent. To the left of the pituitary and continuous with it was a soft, cystic, yellow mass 5 mm. in diameter containing coagulated serum. A narrow rim of pituitary cells persisted and was compressed into a fusiform mass measuring 0.5 by 1 by 2 mm. A few eosinophilic, basophilic and chromophobe cells (figure 10) were demonstrated

in the mass by means of Mallory-Heidenhain stain. The replacing fibrous connective tissue contained a few lymphocytes.

The thoracic portion of the spinal cord showed a mild degree of hydromyelocele.

Comment and Summary

In a case of severe anterior pituitary insufficiency resulting from pituitary atrophy the cause of the pituitary atrophy was not evident; it may have occurred as the result of trauma. The patient weighed less than he did when he was in good health but in no sense of the word was he emaciated or cachectic.

The basal metabolic rate was low and the patient's appearance suggested myxedema. Death resulted from congestive heart failure. The antemortem and postmortem status of the heart was consistent with the diagnosis of myxedema heart. No other cause of heart failure could be demonstrated at necropsy. The coronary arteries and the valves of the heart were normal.

At necropsy the pituitary body, thyroid gland, adrenal cortices and testes were atrophic.

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EDITORIAL

SOME SPECIFIC ANTIMALARIAL DRUGS

ALTHOUGH the drugs which have been in general use are, in most cases, potent in terminating acute attacks of malaria, there are important limitations to their effectiveness and some untoward results attending their administration. Even before the War attempts had been initiated to find more satisfactory specifics. With the advent of the War, the necessity of maintaining armed forces in areas in which malaria is highly endemic as well as the loss of the Dutch East Indies, the only source of quinine in significant quantities, made the problem urgent and acute. Systematic attempts to produce and test new preparations were carried out intensively, both in Great Britain and the United States. Reports of much of the work done in this country have been collected and recently published in a supplementary number of the Journal of Clinical Investigation (May, 1948).

The effect of the antimalarial drugs varies with the different species of malarial parasites and with different strains of the same species. It also differs in the various phases of the life cycle of the parasites and with their location in the body.

When sporozoites are inoculated by the bite of infected mosquitoes, they can be demonstrated in the tissues at the site of the bite and also in the blood provided large amounts are withdrawn within about 20 minutes and transfused into a susceptible subject. They very quickly disappear from the blood, however, and cannot again be so demonstrated until about the eighth day after inoculation (James, Boyd, Fairley). (As a rule they cannot be demonstrated in thick films until two to four days later.) There is still no direct evidence regarding this phase of the life cycle in man. Since the parasites must be undergoing development and multiplication somewhere during this period and since they cannot be demonstrated in the blood, presumably they must be in the tissues. In several species of avian malaria they have been demonstrated in the tissues within endothelial cells in the bone marrow, spleen, brain and other organs. There is a strong presumption (only) that this tissue, or exoerythrocytic, phase also occurs in human and other mammalian malaria. In any event this phase seems to be an essential part of the life cycle. It cannot be materially shortened, even by massive inoculation of sporozoites. How long this tissue phase persists is also not known. There is some presumptive evidence that its duration is protracted and that it is the source of the parasites which cause the repeated relapses, particularly characteristic of quartan and vivax infections.

An ideal drug or combination of drugs for the therapeutic control of malaria should be nontoxic in effective doses and should accomplish the following objectives. (1) It should promptly terminate individual attacks of fever and eliminate the parasites from the blood (asexual cycle), effecting

a temporary cure. (2) It should eliminate the parasites in the tissue phase also, thus preventing relapses and effecting a permanent cure. (3) Used as a prophylactic, in small daily or weekly doses, it should destroy the sporozoites or the organisms in the tissue phase, completely protecting the individual from infection; or, failing this, at least so inhibit their growth that clinical illness does not develop (suppressive effect). (4) It should destroy or devitalize the gametocytes and prevent infection of the mosquito vectors.

A temporary cure in this sense can be accomplished by a number of different drugs. Quinine does this satisfactorily in most cases of infection with all the species affecting man, and it is effective in doses which are not significantly toxic for the great majority of individuals, although minor but often annoying manifestations of cinchonism are common. The value of cinchona and its alkaloids in the treatment of malaria has been demonstrated by about three centuries of experience; and the fact that more potent drugs have been discovered does not lessen its effectiveness or necessarily imply that it has become useless.

Quinine, given prophylactically, is effective as a suppressive agent, but it does not prevent infection. It will cure permanently a significant proportion of cases of falciparum malaria, but it has little effect in preventing relapses in quartan or vivax infections after its administration is stopped. After a varying number of relapses, to be sure, the infection eventually dies out, but the development of an active immunity by the host undoubtedly plays an important part in the cure. This immunity, however, is only temporary, and it is limited to the species and largely to the particular strain of the species involved. Its value in preventing reinfection under natural conditions, therefore, is extremely limited.

The first important addition to the antimalarials (in 1924) was plasmochin (plasmoquine), now commonly termed pamaquine. Although this drug proved too toxic for general use, it showed some significant advantages over quinine. It killed or devitalized the gametocytes (crescents) of falciparum malaria. Although less effective than quinine in controlling an acute attack of malaria, Sinton et al.[1] (1928, 1930) showed that if pamaquine is administered simultaneously with quinine, a synergistic effect was obtained and a permanent cure was effected in many cases of relapsing vivax malaria. Their case material consisted of European soldiers in India, who were suffering from repeated relapses which had not been controlled by quinine alone. Of 64 cases receiving both drugs and observed for eight weeks following treatment, three relapsed, whereas of 38 controls receiving quinine alone, 15 relapsed within this period. Sinton's observations have been confirmed by a number of other observers working with similar case material; e.g., by Piebenga (1930) in Holland; by Manifold (1931) in British-Indian troops; by Thompson and Williams (1945) in British troops in the Medi-

[1] SINTON, J. A., SMITH, S., and POTTINGER, D.: Studies in malaria with special reference to treatment. Part XII. Further researches into the treatment of chronic benign tertian malaria with plasmoquine and quinine, Indian Jr. Med. Research, 1930, xvii, 793–814.

terranean area; and by Most et al.[2] in American troops infected in both the Mediterranean and Pacific theaters. The latter reported relapse rates (clinical or parasitic only) of 89 per cent in 75 cases (all from the Pacific areas) treated with quinine alone; of 84 per cent in 69 cases treated with quinacrine (atabrine) alone; and of 11 per cent of 72 cases treated simultaneously with quinine and pamaquine. (These drugs are not effective if given successively.) The effective doses of pamaquine (.03 to .06 gm. per day), however, caused more or less troublesome toxic reactions in many of the cases, and it would be too dangerous to use except under close medical supervision.

In recent experiments carried out under more rigorous conditions by Berliner et al.[3] the results were less striking but still confirmatory, since five of 18 cases were cured and only two of the others suffered a second relapse.

Pamaquine in full doses will also destroy sporozoites and prevent infection with vivax (and also falciparum) malaria, if it is started the day before experimental infection and continued for a week afterwards. This was shown by James et al.[4] and has been confirmed by Jones et al.,[5] although not all of their cases were protected. The doses required (about .06 gm. per day), however, were far too toxic to warrant its use as a prophylactic agent.

The second important addition to the antimalarial drugs (1930) was atabrine (atebrin, mepaquine), now commonly termed "quinacrine." In brief quinacrine resembles quinine qualitatively in its action and is subject to the same limitations as to its effectiveness. Quantitatively it is more potent as a suppressive and temporarily curative agent, and it is less toxic.[6] No synergistic effect is obtained if quinacrine is combined with quinine. Berliner et al.[3] include in a table four cases of vivax malaria treated with quinacrine and pamaquine concurrently, none of whom relapsed within 10 to 11 months, but they make no comment because the number of observations is so small. It has been generally believed that the administration of quinacrine markedly increases the toxicity of pamaquine, and this is confirmed by Craige et al.[16] (1947) who observed four relapses in five cases so treated. This combination is probably too dangerous to use, even if a synergistic action were demonstrated.

Much of the work done in this country under the guidance of the Board for the Coördination of Malarial Studies was carried out on volunteers who were inmates of the Illinois State Penitentiary at Stateville. These were healthy young adults who were from a nonendemic area and who had not had malaria or an opportunity to develop any immunity from infection.

[2] Most, H., et al.: Combined quinine-plasmochin treatment of vivax malaria: effect on relapse rate, Am. Jr. Med. Sci., 1946, ccxii, 550–560.

[3] Berliner, R. W., et al.: Studies on the chemotherapy of the human malarias. VII. The antimalarial activity of pamaquine, Jr. Clin. Invest., 1948, xxvii, supplementary number, May, part 2, 108–113.

[4] James, S. P., Nicol, W. D., and Shute, P. G.: On prevention of malaria with plasmoquine, Lancet, 1931, ii, 341–342.

[5] Jones, R., Jr., et al.: A study of the prophylactic effectiveness of several 8-aminoquinolines in sporozoite-induced vivax malaria (Chesson strain), Jr. Clin. Invest., 1948, xxvii, supplementary number, May, part 2, 6–11.

The experiments were restricted to a few strains of malarial parasites which had been carefully studied, particularly a strain ("Chesson") of vivax malaria from the Pacific area which had an unusual capacity to cause repeated relapses at short intervals. The technic of the experiments was carefully standardized in every detail, so that the results of many series of experiments were truly comparable. Infection was induced in the natural manner by bites of infected mosquitoes. Many new compounds were synthesized, resembling in chemical structure drugs known to be effective. Those which showed most promise on the basis of curative experiments in avian malaria and tests for toxicity in mammals were similarly studied in human infections. A very few of these which promise to be of practical value will be discussed briefly.

Eighteen compounds were tried[7] which resemble pamaquine in being 8-aminoquinolines. Of these, the best was pentaquine. This drug (like pamaquine) destroyed the sporozoites and completely prevented infection in nine of 10 cases.[5] Of six subjects who developed malaria in spite of the prophylactic use of a drug of this series, four were cured by suppressive drugs (like quinine) which ordinarily are not effective in preventing relapse. Evidently these drugs injured the parasites significantly although not killing them. The dose of pentaquine required to protect, 120 to 180 mg. a day, although less toxic than pamaquine, was still too toxic to permit its use as a prophylactic agent.

Pentaquine is about as effective as quinine in terminating an acute attack of malaria. Its effect is greatly enhanced by the simultaneous administration of quinine. Of 26 subjects with vivax infections of moderate severity, treated with 60 mg. of pentaquine base and 2 gm. of quinine daily for 14 days, only one relapsed, and of 17 cases with severe infections, only three relapsed. Cases with massive infections were not protected from relapse.[8] In these doses some toxic symptoms occurred, but they did not necessitate stopping treatment. Close medical supervision, however, is essential. Smaller, less toxic doses may well prove more practicable for use under ordinary conditions, even though the relapse rate may be slightly higher.

A series of 4-aminoquinolines resembling quinacrine in their structure and activity was also synthesized, and 10 of these were tested on human volunteers by Berliner et al.[9] Of these the best was chloroquine, whose activity was about three times that of quinacrine. Most et al.[10] have reported the results of treatment in 365 cases of vivax malaria in military personnel

[6] TAGGERT, J. V., et al.: Studies on the chemotherapy of the human malarias. V. The antimalarial activity of quinacrine, Ibid., 93–97.

[7] ALVING, A. S., et al.: The clinical trial of 18 analogues of pamaquin [sic] (plasmochin) [sic] in vivax malaria (Chesson strain), Ibid., 34–45.

[8] ALVING, A. S., et al.: Pentaquine (SN-13,276), a therapeutic agent effective in reducing the relapse rate in vivax malaria, Ibid., 25–33.

[9] BERLINER, R. W., et al.: Studies on the chemotherapy of the human malarias. VI. The physiological disposition, antimalarial activity, and toxicity of several derivatives of 4-aminoquinoline, Ibid., 98–107.

[10] MOST, H., et al.: Chloroquine for treatment of acute attacks of vivax malaria, Jr. Am. Med. Assoc., 1946, cxxxi, 963–967.

returned to the United States. As these drugs are stored in the tissues, to get an effective concentration in the blood promptly it is necessary to give a large "priming" dose the first day. The regime recommended consists of two doses (or three [11]) of 0.3 gm. the first day, followed by one dose (0.3 gm.) on each of the succeeding three days. Satisfactory results were also reported following 1.2 gm. in divided doses over a period of 24 hours. These doses are practically nontoxic. All but 2 per cent were afebrile after 24 hours, and films were negative after 48 to 72 hours. Falciparum malaria was cured, but in vivax malaria relapses occurred in about 70 per cent of cases from the Pacific area and in about 35 per cent from the Mediterranean. There is as yet no evidence of a synergistic action when chloroquine is administered with pamaquine. Craige et al.[16] reported four relapses in five cases of vivax infection so treated. Further study of this point is desirable. Chloroquine is effective as a suppressive agent in dose of 0.3 gm. once a week, but it does not prevent infection.

Paludrine, a synthetic biguanidine derivative, is a highly promising drug which was produced and studied by a group of British investigators.[12] It is highly effective in terminating an acute attack of either vivax or falciparum malaria. It will cure falciparum malaria, but cases of vivax infection are prone to relapse, and in this respect it is no better than quinacrine or chloroquine. No synergistic effect was obtained in small series of cases when paludrine was combined with quinine [13] or with pentaquine.[8] It is effective in very small doses. A total dose of 50 to 150 mg. usually sufficed to terminate an acute attack, and 12.5 mg. were effective in some cases. On the other hand, 1.5 gm. per day was administered to some subjects without notable toxic effects. Paludrine appears to be virtually nontoxic in full therapeutic doses.

Its greatest value may prove to be its effectiveness as a prophylactic and suppressive agent.[14] It is a true prophylactic for falciparum malaria, 0.1 gm. per day entirely preventing infection in individuals heavily exposed under natural conditions. Volunteers were similarly protected by a single dose of 1 gm. given three hours before experimental inoculation with mosquitoes. It was equally effective as a suppressive agent in vivax infections, apparently by inhibiting the development of the parasites in the tissue phase without eliminating them. As long as the drug was administered (to individuals who had been exposed to infection while under prophylactic treatment) no symptoms were manifested and no parasites could be demonstrated in the blood, even by transfusion experiments, but clinical malaria developed after the drug was stopped.

[11] Loeb, R. F., et al.: Activity of a new antimalarial agent, chloroquine (SN 7618) (Approved statement), Jr. Am. Med. Assoc., 1946, cxxx, 1069–1070.

[12] Maegraith, B. G., et al.: Paludrine in the treatment of malaria, Brit. Med. Jr., 1946, i, 903–905.

[13] Jones, R., Jr., et al.: The therapeutic effectiveness of large doses of paludrine in acute attacks of sporozoite-induced vivax malaria (Chesson strain), Jr. Clin. Invest., 1948, xxvii, supplementary number, May, part 2, 51–55.

[14] Fairley, N. H., et al.: Researches on paludrine (N. 4888) in Australia, Med. Jr. Australia, 1946, i, 234–236.

These observations have been confirmed in the main by the American group, including Earle et al.[15] They conclude: "The high order of antimalarial activity shown by paludrine against more than a single phase of the malarias, i.e., primary tissue phase of falciparum and erythrocytic phases of vivax and falciparum, places the drug in a unique position among the synthetic antimalarials developed in recent years.

"Paludrine is the most active suppressive agent in vivax malaria yet described, exceeding quinacrine or chloroquine to a considerable extent in this respect.

"It is less active as a suppressive in falciparum malaria, routine suppression at low dosage being due presumably to its high order of prophylactic action in this infection."

One may conclude that chloroquine is clearly superior to quinine and quinacrine in the treatment of an acute attack of malaria, both in effectiveness and in lesser toxicity. Chloroquine seems to be a little more effective than paludrine, in that it terminates the attack somewhat more quickly. Both will cure falciparum malaria, but neither prevents relapses in vivax infections. Because of its almost complete lack of toxicity, paludrine may prove to be the most useful of these drugs under ordinary conditions. Paludrine appears to be distinctly superior to all the other drugs as a prophylactic and suppressive agent. To cure permanently cases of relapsing vivax malaria, the most effective measure at present is the simultaneous administration of quinine and pentaquine. Because of their toxicity, however, this must be done under close supervision, preferably in a hospital, and it is not advised as a routine procedure. A truly ideal antimalarial drug has not yet been found.

P. W. C.

[15] Earle, D. P., Jr., et al.: Studies on the chemotherapy of the human malarias. X. The suppressive antimalarial effect of paludrine, Jr. Clin. Invest., 1948, xxvii, supplementary number, May, part 2, 130–133.

[16] Craige, B., Jr., et al.: Clinical standardization of pamaquin [sic] (plasmochin) [sic] in mosquito-induced vivax malaria, Chesson strain, Am. Jr. Trop. Med., 1947, xxvii, 309–315.

REVIEWS

Brief Psychotherapy: A Handbook for Physicians on the Clinical Aspects of Neuroses. By BERTRAND S. FROHMAN, M.D., with the collaboration of EVELYN P. FROHMAN; foreword by WALTER C. ALVAREZ, M.D. 265 pages; 14 × 20.5 cm. Lea and Febiger, Philadelphia. 1948. Price, $4.00.

This book has been written ostensibly for the benefit of the non-psychiatric physician, to help him treat his neurotic patients. More than two-thirds of the volume presents a simplified description and discussion of the common neuroses, their etiology and their mechanisms. This part is too simplified and contains so many inaccurate statements which do not fit accepted psychiatric theory that the reviewer feels the book would mislead rather than aid the practicing physician. The remainder describes methods of brief treatment which would take years of training and specialized experience for a therapist to use successfully. For these reasons this book is not "A Handbook for Physicians" as the sub-title indicates.

H. W. N.

Medical Writing: The Technic and the Art. 2nd Ed. By MORRIS FISHBEIN, M.D., with the assistance of JEWEL F. WHELAN, Assistant to the Editor. x plus 292 pages; 23.5 × 15.5 cm. 1948. The Blakiston Company, Philadelphia. Price, $4.00.

Physicians and scientific writers who have had constant use for the first edition of this book, published ten years ago, will welcome the enlarged and revised second edition. Developed as a result of experience with the many manuscripts and periodicals published by the American Medical Association, the material includes help in the construction, preparation and revision of the manuscript, spelling, style and proofreading. The chapter on "Indexing" is new, and that on "Illustrations" has been extensively revised.

Not only will the physician who prepares articles for publication want this book for reference, but he will find it interesting reading as well.

M. L. W.

The Contemporary American Family. By ERNEST R. GROVES and GLADYS HOAGLAND GROVES. 838 pages; 15 × 22.5 cm. J. B. Lippincott Co., Philadelphia. 1947. Price, $4.50.

The late Dr. Groves and Mrs. Groves designed this comprehensive study, "The Contemporary American Family," to be useful to the reader in his personal career. The book is pedagogic, yet palatable. In surveying their subject through the eyes of history, psychology, sociology, law, biology, mental hygiene, home economics, and education, the authors sacrificed clarifying detail for breadth of scope. It would be useful as a college textbook and for beginning students who wish to study the American Family.

H. W. N.

The Development of Inhalation Anesthesia (with Special Reference to the Years 1846–1900). By BARBARA M. DUNCUM, Nuffield Department of Anesthetics, University of Oxford. 640 pages; 14.5 × 23 cm. Oxford University Press, New York. 1947. Price, $12.00.

This book, after a brief introduction which outlines and correlates the body of the text, presents a detailed account of the history of inhalation anesthesia from the

middle of the 16th century to the beginning of the modern era in the first decade of the 20th century.

The author, after touching upon the early experiments of Harvey and von Helmont on the physiology of respiration, discusses briefly the discoveries of oxygen, carbon dioxide, nitrous oxide, etc., and then enlarges upon the important work of W. T. G. Morton, James Simpson, Horace Wells and Crawford Long. Following this, and in great detail, the problems and controversial issues regarding the use of ether on the one hand and chloroform on the other are discussed, along with the efforts of all men interested in anesthesia to develop other and more perfect agents and technics.

Especially interesting are the excellent illustrations and descriptions of apparatus, and the original correspondence and reports of such men as John Snow, James Simpson and Joseph Clover, pioneers in anesthetic specialization.

This book, because of its great detail, rather than in spite of it, makes absorbing reading.

A. T. N.

BOOKS RECEIVED

Books received during August are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Advances in Pediatrics. Volume III. Editorial Board: S. Z. LEVINE, Cornell University Medical College; ALLAN M. BUTLER, Harvard Medical School; L. EMMETT HOLT, JR., New York University, College of Medicine; and A. ASHLEY WEECH, University of Cincinnati, College of Medicine. 363 pages; 24 × 16 cm. 1948. Interscience Publishers, Inc., New York. Price, $7.50.

Bacterial and Virus Diseases: Antisera, Toxoids, Vaccines and Tuberculins in Prophylaxis and Treatment. By H. J. PARISH, M.D., F.R.C.P.E., D.P.H., Clinical Research Director, Wellcome Foundation, Ltd., etc. 168 pages; 19 × 12.5 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, $2.75.

Breast Feeding: A Guide to the Natural Feeding of Infants. By F. CHARLOTTE NAISH, B.A., M.B., B.Ch. (Cantab.) 151 pages; 19 × 13 cm. 1948. Oxford University Press, New York. Price, $3.50.

Essentials of Pathology. 3d Ed. By LAWRENCE W. SMITH, M.D., F.C.A.P., Formerly Professor of Pathology, Temple University School of Medicine, etc., and EDWIN S. GAULT, M.D., F.C.A.P., Associate Professor of Pathology and Bacteriology, Temple University School of Medicine. With a Foreword by the late JAMES EWING, M.D., Memorial Hospital, New York City. 764 pages; 27.5 × 21 cm. 1948. The Blakiston Company, Philadelphia. Price, $12.00.

An Index of Treatment by Various Writers. 13th Ed., Revised. Edited by SIR ROBERT HUTCHISON, Bt., M.D., LL.D., F.R.C.P., Consulting Physician, London Hospital, etc.; Assisted by REGINALD HILTON, M.A., M.D., F.R.C.P., Physician to St. Thomas's Hospital, etc. 972 pages; 26 × 17 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, $17.00.

Major Endocrine Disorders. 2nd Ed. By S. LEONARD SIMPSON, M.A., M.D. (Cantab.); F.R.C.P. (London), Physician, Willesden General Hospital, with Charge of Diabetic and Endocrine Clinics, etc. Foreword to the First Edition by the late SIR WALTER LANGDON-BROWN, M.A., M.D. (Cantab.); F.R.C.P. (London), Emeritus Professor of Physic in the University of Cambridge. 552 pages; 22.5 × 14 cm. 1948. Oxford University Press, New York. Price, $14.00.

Manual of Leprosy. By ERNEST MUIR, C.M.G., C.I.E., M.D., F.R.C.S., Edin., Medical Adviser, British Empire Leprosy Relief Association, etc. 208 pages; 22 × 14 cm. 1948. The Williams and Wilkins Company, Baltimore. Price, $5.00.

Medical Writing: The Technic and the Art. 2nd Ed. By MORRIS FISHBEIN, M.D., with the assistance of JEWEL F. WHELAN, Assistant to the Editor. x plus 292 pages; 23.5 × 15.5 cm. 1948. The Blakiston Company, Philadelphia. Price, $4.00.

More Than Armies: The Story of Edward H. Cary, M.D. By BOOTH MOONEY. With an Introduction by DR. MORRIS FISHBEIN. vii plus 275 pages; 22.5 × 15 cm. 1948. Mathis, Van Nort & Company, Dallas. Price, $5.00.

Recent Advances in Anaesthesia and Analgesia (Including Oxygen Therapy). 6th Ed. By C. LANGTON HEWER, M.B., B.S. (Lond.), M.R.C.P. (Lond.), D.A. (Eng.), Senior Anaesthetist, St. Bartholomew's Hospital, etc. 380 pages; 21 × 14 cm. 1948. The Blakiston Company, Philadelphia. Price, $6.00.

The Social Medicine of Old Age: Report of an Inquiry in Wolverhampton. By J. H. SHELDON, M.D. (London), F.R.C.P. (London), Director of Medicine, The Royal Hospital, Wolverhampton. 239 pages; 21.5 × 14 cm. (paper-bound). 1948. Oxford University Press, New York. Price, $2.00.

Standards for the Diagnosis and Treatment of Cancer. By THE CANCER COMMITTEE OF THE IOWA STATE MEDICAL SOCIETY. 160 pages; 23.5 × 15.5 cm. (stiff-paper back). 1948. Iowa State Medical Society, Cedar Rapids. Price, $1.00.

The Treatment of Malignant Disease by Radium and X-Rays, Being a Practice of Radiotherapy. By RALSTON PATERSON, M.C., M.D., F.R.C.S.E., D.M.R.E., F.F.R., Christie Hospital and Holt Radium Institute, Manchester. 622 pages (and charts); 25 × 17 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, $11.00.

Tuberculosis in the British Zone of Germany, with a Section on Berlin. Report of an Inquiry Made in September-October, 1947. By M. DANIELS, M.D., D.P.H., and P. D'ARCY HART, M.D., F.R.C.P., Members of the Scientific Staff Medical Research Council. 32 pages (and 37 pages in Berlin section); 24.5 × 15.5 cm. (paper-bound). 1948. His Majesty's Stationery Office, London. Price, Sixpence net.

Zinsser's Textbook of Bacteriology: The Application of Bacteriology and Immunology to the Diagnosis, Specific Therapy and Prevention of Infectious Diseases for Students and Practitioners of Medicine and Public Health. 9th Ed. Revised by DAVID T. SMITH, M.D., Professor of Bacteriology and Associate Professor of Medicine, Duke University School of Medicine; DONALD S. MARTIN, M.D., M.P.H., Professor of Preventive Medicine and Public Health and Associate Professor of Bacteriology, Duke University School of Medicine; NORMAN F. CONANT, Ph.D., Professor of Mycology and Associate Professor of Bacteriology, Duke University School of Medicine; JOSEPH W. BEARD, M.D., Professor of Surgery in Charge of Experimental Surgery, Duke University School of Medicine; GRANT TAYLOR, M.D., Associate Professor of Bacteriology and Associate Professor of Pediatrics, Duke University School of Medicine; HENRY I. KOHN, Ph.D., M.D., Surgeon U. S. P. H. S., Assistant Professor of Physiology and Pharmacology (on leave), Duke University School of Medicine; and MARY A. POSTON, M.A., Instructor in Bacteriology, Duke University School of Medicine. 992 pages; 25.5 × 17 cm. 1948. Appleton-Century-Crofts, Inc., New York. Price, $10.00.

COLLEGE NEWS NOTES

A.C.P. Postgraduate Courses, Autumn 1948

At this date (September 13, 1948) the Autumn schedule of courses is well launched.

Course No. 1, Cardiology, at the National Institute of Cardiology of Mexico, under Dr. Ignacio Chavez, F.A.C.P., Director, has been concluded. Twenty-three American physicians were registered, many were accompanied by members of their families, and arrangements were made for a combined postgraduate course and vacation. Dr. E. L. Bortz, F.A.C.P., Philadelphia, Chairman of the Advisory Committee on Postgraduate Courses, was in attendance throughout the period. The physical accommodations were superior to those of any institution where similar courses have been given previously. The course was so arranged that approximately one-half of the morning was devoted to didactic teaching and one-half to clinical teaching in groups of three or four physicians. Dr. George R. Herrmann, F.A.C.P., Professor of Medicine at the University of Texas School of Medicine, was a guest teacher from the States. All the Mexican teachers spoke English so there were no language difficulties. Reports from the registrants in the course indicate superb arrangements and most excellent teaching, with great credit going to the Director, Dr. Chavez. It is hoped that with this excellent beginning, the College will arrange not only to repeat this course but to schedule other courses occasionally in Mexico City.

Course No. 2, Internal Medicine with Emphasis on Pathological Physiology, September 13–18, at the University of Cincinnati College of Medicine under Dr. M. A. Blankenhorn, F.A.C.P., Director, was over-subscribed and a number of members, and many non-members, who wished to take the course could not be accommodated this year. That course is at this time still in progress.

Course No. 3, Internal Medicine, September 20–October 2, at the University of Pittsburgh Medical Center under Dr. R. R. Snowden, F.A.C.P., Director, was first scheduled for a maximum of 25, but demand was so great among members of the College for this course, which has already developed an outstanding reputation from previous years, that arrangements were made whereby the number could be increased to 47.

Course No. 4, Internal Medicine, October 18–29, at the University of Michigan Medical School under Dr. Cyrus C. Sturgis, F.A.C.P., Director, is at this time still in process of registration. It is anticipated that a very satisfactory registration will develop for this course.

Course No. 5, Endocrinology, November 1–6, under the auspices of the University of Illinois College of Medicine, but with headquarters at the LaSalle Hotel, Chicago, is still in the process of registration and there are facilities available for a number more registrants. A group of as many as 100 can be accommodated. This course has been given by the College on several previous occasions and has always been an outstanding success. It includes an intensive review of new developments in the field of endocrinology, special attention to be paid to clinical disorders. Physiological and biochemical developments will be presented in relation to their bearing on the interpretation of clinical phenomena. A great host of institutions and societies are represented on the faculty; in fact, there probably has never before been a course offered by the College with such an array of teachers from all over the U. S. and Canada. Detailed outlines of all features of the course are available and those interested should register immediately. Hotel and other accommodations are adequately available.

Course No. 6, Recent Advances in the Diagnosis and Treatment of Cardiovascular Disease, November 15–24, at the Massachusetts General Hospital under

Drs. Paul D. White, F.A.C.P., Howard B. Sprague, F.A.C.P., and Edward F. Bland, Directors, as usual, has been filled to capacity for some weeks. In fact, the maximum accommodations were increased from 90 to 100 and even then a very large number of late applicants could not be accommodated. The reputation of this course is expanding far beyond the U. S. and Canada as evidenced by applications from European countries, India, Puerto Rico and elsewhere. Those who could not be accommodated this year will be placed on a waiting list to receive preference for registration the next time this course is given, presumably in the Autumn of 1949.

Course No. 7, CARDIOVASCULAR DISEASE, December 6–11, at Emory University School of Medicine, Atlanta, Ga., under Dr. R. Bruce Logue, F.A.C.P., Director, is still in the course of registration. The maximum number that can be accommodated has been raised from 50 to 75. The local faculty will be ably assisted by Dr. Eugene A. Stead, Jr., F.A.C.P., Professor of Medicine at Duke University School of Medicine, and by Dr. Richard L. Riley, Research Associate, Columbia University College of Physicians and Surgeons, New York. During recent years, a considerable knowledge of the cardiovascular system has accumulated through the use of newer technics, such as catheterization and contrast visualization, as well as studies with the use of radioactive isotopes. The practical application of the studies will be given and a brief survey of electrocardiography with emphasis on recent developments will be included. Detailed outlines of this course are available on request. The course is a very excellent one in its field and a tribute to the fine work being done at this southern institution.

Course No. 8, GASTRO-ENTEROLOGY, December 6–11, at the Graduate Hospital of the University of Pennsylvania, Philadelphia, under Dr. Henry L. Bockus, F.A.C.P., Director, was originally scheduled for a maximum number of 55 physicians. The demand has been so great that a careful survey revealed that a larger number could be accommodated and the Director is prepared now to accommodate 100 registrants. The course includes a survey of recent and significant developments in gastro-enterology. Emphasis throughout the course will be placed on gastrointestinal physiology, biochemistry and pathology. There will be didactic presentations, conferences, case reports, and panel discussions. Features have been carefully selected and the instructors will be members of the faculties of many nearby medical schools in addition to those on the faculty of the University of Pennsylvania. The Director is a most capable and inspiring teacher.

Address all inquiries and applications for registration to Mr. E. R. Loveland, Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

A.C.P. REGIONAL MEETINGS

1948–49

Date	*Territory*	*Place*	*Chairman*
July 25	Mississippi	Jackson, Miss.	John G. Archer, M.D., *Governor*
September 11	North Dakota	Fargo, N. D.	R. B. Radl, M.D., *Governor*
September 25	Oklahoma	Tulsa, Okla.	Wann Langston, M.D., *Governor*
September 29	Western Pennsylvania	Pittsburgh, Pa.	R. R. Snowden, M.D., *Governor*
October 20	Western New York	Syracuse, N. Y.	E. C. Reifenstein, M.D., *Governor*

October 30	Arkansas	Hot Springs, Ark.	Arless A. Blair, M.D., *Governor*
November 5	New Jersey	Newark, N. J.	George H. Lathrope, M.D., *Governor*
November 12–13	NORTHWEST: Washington, Oregon, Wyoming, Alberta, British Columbia, Manitoba, Saskatchewan, Idaho, Montana	Vancouver, B. C.	G. F. Strong, M.D., *Regent*
November 20	MIDWEST: Michigan, Illinois, Indiana, Wisconsin	Detroit, Mich.	Douglas Donald, M.D., *Governor*

In addition, Regional Meetings are being planned for Iowa in October, the exact date and place yet to be determined by B. F. Wolverton, M.D., Governor; for Kentucky, under the Governorship of J. Murray Kinsman, M.D., in November or December; and for Maryland and the District of Columbia. Drs. Wetherbee Fort and Wallace M. Yater, Governors for these two territories, respectively, are discussing the possibility of holding the meeting this year in Washington, D. C. Place and date will be announced later.

The program of the Western Pennsylvania Regional Meeting included scientific sessions in the morning and afternoon at the Western State Psychiatric Institute and Clinic, and an evening session at the Pittsburgh Athletic Association Annex. The morning symposium concerned Rheumatic Fever, and the participants were Frank J. Gregg, M.D., F.A.C.P., Grace S. Gregg, M.D., and J. J. McAleese, M.D., all of Pittsburgh. The afternoon session offered a symposium on Viruses and Virus Diseases, with discussions by Byron L. Bennett, (MC), USA, Ret'd, Max A. Lauffer, Ph.D., W. Conway Price, Ph.D., and Jonas E. Salk, M.D., all of Pittsburgh. Cocktails and a banquet followed, with musical offerings and remarks by the local Governor, R. R. Snowden, M.D., F.A.C.P., by Edward L. Bortz, M.D., F.A.C.P., Governor for Eastern Pennsylvania, by William S. McEllroy, M.D., F.A.C.P., Dean of the University of Pittsburgh School of Medicine, and by E. R. Loveland, A.C.P. Executive Secretary.

Members of the College from Western New York met on October 20 at the Syracuse University College of Medicine and the Onondaga Golf and Country Club. The following papers were presented in the scientific sessions: Basic Studies with Vitamin E, by John R. Williams, Sr., M.D., F.A.C.P., Rochester; Pitfalls in the Diagnosis of Diabetes, Bernard A. Watson, M.D., F.A.C.P., Clifton Springs; Vasodepressor Properties of Morphine when Administered Following Hypotension, Richard Lee, M.D., Syracuse; Bacterial Endocarditis with Emphasis on Escherichieae-Aerobacter Group as the Infective Organism, C. Stewart Wallace, M.D., Associate, Ithaca; Detection of Blocking Antibody by the Direct Method in Patients with Ragweed Hay Fever, William G. Woodin, M.D., Syracuse; Significance of Axis Deviation, George H. Reifenstein, M.D., Associate, Syracuse; Results of Cardiorespiratory Functional Studies in Cases of Beryllium Granulomatosis of the Lung, Robert Bruce, M.D., Rochester; Significance of Human Adrenal Cholesterol in Relation to Adrenal Function and Morphology, Walter F. Rogers, M.D., Syracuse; Utilization of Human Albumin, Christine Waterhouse, M.D., Rochester; Changes in Peripheral Blood Flow after Sympathetic Blockade and Sympathectomy, Richard H. Lyons, M.D., F.A.C.P., Syracuse; Renal Factors in the Formation of Edema, Robert F. Pitts, M.D., F.A.C.P., Syracuse; Multiple Angiomata of the Lungs Simulating Congenital Heart Disease, William S. McCann, M.D., F.A.C.P., Rochester; Diagnosis and Treatment of Gouty Arthritis, John H. Talbott, M.D., F.A.C.P., Buffalo. The papers presented were

discussed by A.C.P. President Walter W. Palmer, of New York City, following which J. Howard Ferguson, M.D., of Syracuse, led a clinical pathological conference, with discussion by Edward N. Packard, M.D., F.A.C.P., Trudeau, and Frederick T. Schnatz, M.D., F.A.C.P., Syracuse. Dr. Palmer was the chief speaker in the evening, but brief remarks were made also by Dr. McCann, Dr. Asa L. Lincoln, Governor for Eastern New York, Dr. H. G. Weiskotten, Dean of Syracuse University College of Medicine, and Mr. E. R. Loveland, Executive Secretary.

At the time of this writing, only the tentative program of the Northwest Regional Meeting, Vancouver, B.C., November 12–13, can be given. Papers were presented by the following physicians, in the Vancouver General Hospital: Cardiac Complications of Infectious Mononucleosis, Hance F. Haney, M.D., Associate; Hiatus Hernia, John H. Fitzgibbon, M.D., F.A.C.P.; Sarcoidosis, John J. Krygier, M.D., Associate; Inhibitory Hormone of the Testicle, Ben Vidgoff, M.D., Associate; Congestive Heart Failure, Particularly Splenomegaly in That Condition, Isidor C. Brill, M.D., F.A.C.P.; Discussion of the Lymphomatous Diseases, Russel L. Baker, M.D., F.A.C.P.; Use of Vitamin E in Arteriosclerotic Heart Disease, Homer P. Rush, M.D., F.A.C.P.; all of Portland, Ore.; Ankylosing Spondylitis, Kenneth A. Hamilton, M.D., F.A.C.P., Edmonton, Alta.; Medical Aspects of Atomic Energy, Stafford L. Warren, M.D., Los Angeles, Calif.; Primary Tuberculous Skin Infection from a Swimming Pool, Donald E. H. Cleveland, M.D., F.A.C.P.; Somatic or Psychic?, George A. Davidson, M.D., F.A.C.P.; Role of the Failing Heart in Cerebral Thrombosis, George F. Strong, M.D., F.A.C.P., and Samuel E. C. Turvey, M.D., F.A.C.P.; all of Vancouver, B. C.; Consideration of the Pathology of Pyelonephritis in Application of Therapy, Robert H. Williams, M.D., F.A.C.P.; and Metabolic Aspects of Hypertensive Disease, Daniel M. Green, M.D., F.A.C.P.; both of Seattle, Wash. The sessions were presided over by Dr. Charles E. Watts, F.A.C.P., Seattle, Third Vice President, Dr. John W. Scott, M.D., F.A.C.P., Edmonton, Governor for Alberta and British Columbia, and by the Governor for Washington, Dr. George H. Anderson, M.D., F.A.C.P., of Spokane. Guest speakers listed for the evening session at the Hotel Vancouver included A.C.P. President Walter W. Palmer, of New York, Mr. E. R. Loveland, Executive Secretary, Philadelphia, and Dr. L. R. Donaldson, Associate Professor of Fisheries, University of Washington.

University of Michigan Announces 1949 Postgraduate Course Schedule

Dr. Howard H. Cummings, Chairman and Professor in the Department of Postgraduate Medicine, University of Michigan, announces the following schedule of courses during 1949. Further information can be obtained by addressing Dr. Cummings.

1. Application of the Basic Sciences to Clinical Medicine; January 3–29.
2. Diseases of the Gastro-Intestinal Tract; March 14–18.
3. Metabolism and Endocrinology; March 21–25.
4. Rheumatology and Recent Advances in Therapeutics; March 28–April 1.
5. Diseases of the Heart; April 4–8.
6. Diseases of the Blood and Blood-Forming Organs; April 11–15.
7. Allergy; April 18–22.

University of California at Los Angeles Announces Postgraduate Course Program

Dr. S. J. Weinberg (Associate, ACP), Head of Postgraduate Instruction, Medical Extension, University of California, Los Angeles, has announced the program of postgraduate courses for 1948–49, as follows:

INFECTIOUS DISEASES; October 21, 1948–March 31, 1949; Thursdays, 8:00 to 10:00 p.m.

DERMATOLOGY IN INTERNAL MEDICINE; January 3–February 21, 1949; Mondays, 8:00 to 10:00 p.m.

MEDICINE; September 21–December 7, 1948; Tuesdays, 8:00 to 10:00 p.m.

CARDIOLOGY; September 22–December 8, 1948; Wednesdays, 8:00 to 10:00 p.m.

PEDIATRICS; September 23–December 2, 1948; Thursdays, 8:00 to 10:00 p.m.

ELECTROCARDIOGRAPHY; January 4–20, 1949; Tuesdays and Thursdays, 8:00 to 10:00 p.m.

MEDICAL PHOTOGRAPHY; September 20, 1948, four different meeting hours, 8:00 to 10:00 p.m.

NEUROPSYCHIATRY FOR THE GENERAL PRACTITIONER; October 1–December 10, 1948; Fridays, 8:00 to 10:00 p.m.

SURGICAL PATHOLOGY; to be given during spring of 1949.

All courses on the above schedule will be held at Los Angeles.

AMERICAN GOITER ASSOCIATION

The next annual meeting of the American Goiter Association will be held May 26–28, 1949, at the Hotel Loraine, Madison, Wis. The program will include papers on goiter and other diseases of the thyroid gland, dry clinics and demonstrations.

The Van Meter Prize Award of $300.00 and awards of two honorable mentions will be made for the best essays concerning original work on problems related to the thyroid gland. Competing essays may cover either clinical or laboratory investigations and should be submitted not later than March 15, 1949, as typewritten double space copy, in English, to the Corresponding Secretary, Dr. T. C. Davison, 207 Doctors Building, Atlanta 3, Ga. The papers should not exceed 3,000 words in length.

NATIONAL DIABETES WEEK
December 6–12, 1948

The Committee on Diabetes Detection of the American Diabetes Association has initiated far reaching plans for a National Diabetes Detection Week, December 6–12, 1948. The discovery and treatment of diabetes mellitus at an early stage demands the attention of all practicing physicians. Failure to discover and treat diabetes early results in preventable disabilities and impairments of health. In the Diabetes Exhibit before the last meeting of the American Medical Association at Chicago, it was shown that the mortality rate for diabetics first seen when a complication had occurred was three times the rate for diabetics first seen earlier and before impairments had developed.

Dr. Charles H. Best, as President of the American Diabetes Association, is urging the coöperation of all medical societies, county, state and national, to support the plans for the National Diabetes Week. The National Committee on Diabetes Detection has prepared material containing information on diabetes for use by the physician in his own town. This material includes programs for medical meetings, radio broadcasts and spot radio announcements for use by city and county medical societies, and suggestions for coöperation with local hospitals toward the control of diabetes.

The Executive Committee of the Menninger Foundation School of Psychiatry (psychiatric teaching division of the Institute of Psychological Medicine) and the Winter Veterans Administration Hospital of Topeka are accepting applications for admission to the School on January 1, 1949, available only to doctors who have had

some psychiatric residency training in an approved hospital, and who can, therefore, qualify for advanced standing. Dr. Karl Menninger is the Chairman of the Dean's Committee of the School, and Dr. William C. Menninger, F.A.C.P., has much to do with the teaching and the direction of the training program.

According to the minutes of the meeting of the Joint Committee for the Coördination of Medical Activities held in Chicago, June 5, a new specialty board has been organized to establish standards and meet the needs of physicians engaged in full-time careers in preventive medicine and public health. The board will consist of nine members—three from the American Public Health Association, three from the Section on Preventive and Industrial Medicine for Public Health of the American Medical Association, one from the Southern Medical Association, one from the Canadian Public Health Association, and one from the University Schools of Public Health. The new board will be called the American Board of Preventive Medicine and Public Health Physicians.

The New York Academy of Medicine Conducts Twenty-First Graduate Fortnight

The Twenty-First Graduate Fortnight of the New York Academy of Medicine was conducted at the Academy Building from October 4 to 15, 1948, on the general subject of "Advances in Therapy." President of the Academy is Dr. George Baehr, F.A.C.P. Dr. Mahlon Ashford, F.A.C.P., was Chairman of the Committee on Hospital Clinics, and Dr. Louis J. Soffer, F.A.C.P., was Chairman of the Committee on Panel Discussions. A large percentage of the speakers on the program were Fellows of the American College of Physicians.

International Society of Internal Medicine

Professor A. Gigon of Basel, Switzerland, who has been active in the plans for the organization of the International Society of Internal Medicine, has reported (September 1, 1948) that the following countries will be represented at the first meeting at Basel, September 27–29: Austria, Belgium, Czechoslovakia, Denmark, Finland, France, Great Britain, Holland, Hungary, Italy, Norway, Portugal, Spain, Sweden, Switzerland, Turkey, United States of America; and, possibly, some South American countries, Australia, Canada, China and India.

Dr. Thomas T. Holt, of Wichita, the first Fellow of the American College of Physicians from the State of Kansas (1923), retired from active practice July 14, 1948. Dr. Holt was very active in the affairs of the College as College Governor for Kansas from 1929 to 1941, and as Vice President, 1941–42. He was one of the original proponents of each state having its own regional meeting and was very successful in devoting approximately one-half of his program to the basic sciences. This has become an avowed part of the postgraduate program of the College, as represented by various courses given in recent years on the physiologic approach to medicine. Dr. Holt, himself, took approximately 22 postgraduate courses the first half of his medical life, extending from a minimum of one month to one year and taken in the various medical centers of Europe as well as throughout the states.

F. William Sunderman, M.D., F.A.C.P., has recently been appointed head of the Department of Clinical Pathology of the Cleveland Clinic Foundation. Formerly a member of the Medical Faculty of the University of Pennsylvania School of Medicine and Assistant Director of the University Hospital's Pepper Laboratory, Dr. Sunderman has more recently served as Professor of Clinical Pathology and Director of the

Laboratory of Clinical Medicine in the Temple University Medical School. Dr. Sunderman is a Diplomate of the American Board of Pathology and the American Board of Internal Medicine. He serves as a member of the American Board of Trustees of the American Board of Pathology, a Governor of the College of American Pathologists, and a member of the editorial board of the American Journal of Clinical Pathologists.

Colonel A. Parker Hitchens, (MC), U. S. A., Ret'd, F.A.C.P., has recently resigned from his position as Health Commissioner, Wilmington, Del., to become Director of the Bureau of Laboratories of the Pennsylvania State Department of Health. His office is located in the Laboratories of Public Health and Preventive Medicine Bldg. on the campus of the University of Pennsylvania.

Brigadier General Leon A. Fox, (MC), U. S. A., Retired, F.A.C.P., has been honored by a decoration of Honorary Commander of the Order of the British Empire. The citation mentions the valuable assistance which General Fox gave to the British armies as Field Director of U. S. Typhus Commission.

John D. Battle, M.D., (Associate), Cleveland, has been appointed a member of the staff of the Cleveland Clinic in the Division of Internal Medicine. Dr. Battle graduated from Washington and Lee University in 1934, and received his M.D. degree from the University of Pennsylvania in 1938. A diplomate of the American Board of Internal Medicine, Dr. Battle was a Fellow at the Cleveland Clinic from 1940 to 1942.

Dr. Robert B. Radl, F.A.C.P., College Governor for North Dakota, was recently appointed to a 3-year term on the State Board of Medical Examiners of North Dakota.

Dr. Leon Hughes Hetherington, F.A.C.P., heretofore in the Veterans Administration, has been appointed Director of Tuberculosis Services in the State Department of Health in the State of Maryland, effective October 1, 1948, and will have his headquarters at 2411 North Charles Street, Baltimore, Md.

Harry Warshawsky, M.D., F.A.C.P., resigned from full-time service in the Veterans Administration in June and has since become established in the private practice of internal medicine in Lima, Ohio.

Brigadier General Henry C. Dooling, F.A.C.P., has recently retired from the U. S. Army and is now Medical Director of State Sanitorium No. 1, South Mountain, Pa.

Philip Krainin, M.D., F.A.C.P., New York, has been appointed Assistant Clinical Professor of Medicine in the New York Medical College.

Carrol C. Turner, M.D., F.A.C.P., Memphis, has gained considerable recognition as an amateur photographer. He received the Silver Cup of the American Physicians' Art Association during the recent American Medical Association meeting in Chicago, an honor which he won also in 1946. His rating among salon exhibitors in the 1948 issue of American Annuals of Photography was 23rd and during the last five years he had 291 prints hung in 160 International Salons, making him a "Three Star Exhibitor."

Louis H. Bauer, M.D., F.A.C.P., Hempstead, N. Y., has been elected Executive Secretary of the World Medical Association, the offices of which have been established at the New York Academy of Medicine.

Glenn E. Drewyer, M.D., F.A.C.P., formerly on the staff of the Glenwood Hot Springs Clinic, Glenwood Springs, Colo., has recently accepted appointment as Clinical Director of the Veterans Administration Center at Bay Pines, Fla. Dr. Drewyer will reside at 206 15th Ave., N. E., St. Petersburg, Fla.

Dr. Alfred W. Dubbs, F.A.C.P., has recently been appointed as head of the Department of Medicine, Sacred Heart Hospital, Allentown, filling the vacancy created by the death of Dr. Willard D. Kline, F.A.C.P. Dr. Dubbs has been an Associate in Medicine at the Sacred Heart Hospital since 1935, and Director of the Department of Cardiovascular Disease since 1937.

A very interesting account of the development and organization of a large industrial medical department is given in the Thirtieth Anniversary Issue of The Medical Bulletin of Standard Oil Company (New Jersey) and Affiliated Companies, Vol. 8, No. 2, June, 1948. This number also pays tribute to Willard J. Denno, M.D., F.A.C.P., New York, N. Y., in the following statement.

"Under the constant vigilance and guidance of Dr. Willard J. Denno, the medical department grew during his twenty-seven years of service into a world-wide organization. He has shown what can be done in the medical phase of human relations when the utmost support of Management is received. His greatest contribution to medicine in industry was his broad vision in foreseeing the requirements of a medical department in order for it to assume its proper role in the affairs of a modern-day business enterprise. It is mainly due to his unusual quality of leadership and ability to organize and coördinate the diversified medical activities of the parent organization that the present status of the medical departments has been attained."

OBITUARIES

DR. BERTHOLD STEINBACH POLLAK

Dr. Berthold S. Pollak died June 27, 1948, one day after his seventy-fifth birthday, of cerebral arteriosclerosis. He was born June 26, 1873, in Vienna, the son of Theresa and Joseph Pollak, and came to the United States when 15 years old. For three years he was an apprentice in the Philadelphia wholesale drug firm of Bullock and Crenshaw, after which he attended the Philadelphia College of Pharmacy and the University of Pennsylvania. He graduated in Medicine from Dartmouth College in 1895, served as assistant to his uncle, the late Dr. Louis Steinbach, professor of surgery at the Philadelphia Polyclinic Hospital, and subsequently was chief resident physician at the Pottsville Hospital, Pottsville, Pa. In 1896 Dr. Pollak married Miss Henrietta G. Cohn of Pottsville, Pa., who died in 1912. In 1917 he married Miss Louise Gruber of Baltimore, Md., who died in 1937. He leaves two daughters, Mrs. Philip S. Birnbaum of Jersey City and Mrs. Alfred Kruger, wife of Dr. Kruger, of Norfolk, Va., and three grandchildren.

Arriving in Jersey City in 1898, as a young general practitioner, he soon became the physician to many of the most prominent families. Because of his strong personality and unusual oratorical ability, he was promptly recognized as a leading figure in community welfare work. When, in 1907, plans began to develop for a tuberculosis sanatorium in Hudson County, Dr. Pollak was chosen to head it. He was sent abroad to glean from the famous tuberculosis centers the latest and best in diagnosis and treatment. In due time he succeeded in organizing a sanatorium at Secaucus, followed by a chain of diagnostic chest clinics throughout the County that now serve as diagnostic stations for chest diseases. In this capacity they also provide a consultation service to private physicians and cover most of the follow-up in the findings of mass surveys.

With the newer developments in the treatment of tuberculosis Dr. Pollak soon saw the advantages of having a tuberculosis hospital in or near a large city. He felt that not only was the institution nearer the patient's family, but also located where leading specialists were more available. This long-hoped-for desire of his was realized when the new three million dollar tuberculosis hospital was erected in 1937 as the Hudson County Tuberculosis Hospital. In view of his 40 years of devotion and leadership in the fight against tuberculosis this hospital was renamed in his honor in 1946 as the Berthold S. Pollak Hospital for Chest Diseases. Through his efforts the hospital was then opened also to those needing special treatment for chest diseases other than tuberculosis. Until a qualified clinic staff was acquired, he personally looked after many of the clinics, including night clinics while these were in force. He also served as consulting phthisiologist to nearly all the hospitals in Hudson County, the Beth Israel Hospital in Newark, and served as chairman of the Medical Board of Deborah Jewish Consumptive Sanatorium at Browns Mills, N. J.

In 1919, he helped organize the Hudson County Tuberculosis League and, up to his last illness, served as a leading force in its accomplishments. Largely through his efforts in the League and as chairman of the Legislative Committee of the Medical Society of New Jersey, a law was passed in 1939 making tuberculin test of school children mandatory for the first time in this country. This has since practically eliminated tuberculosis in high schools and colleges in New Jersey and created a wholesome tuberculosis consciousness of the public in general with a better understanding of the entire problem.

One of the earliest members of the American College of Physicians, having been elected a Fellow in 1916, Dr. Pollak was also a Fellow of the American Medical Association, a Diplomate of the American Board of Internal Medicine, a past president

of the Hudson County Medical Society, the New Jersey Tuberculosis League, and the New Jersey Public Health and Sanitary Association, and a delegate of the National Tuberculosis Association at conferences of the International Union against Tuberculosis in London, Paris, Lausanne, Brussels, Oslo, Warsaw, Rome, Lisbon and Washington. He was the author of many articles on various phases of early diagnosis and treatment of tuberculosis. In all these activities he displayed broad constructive ideas backed by a ruggedness of body and spirit that enabled him to carry on until the wear and tear of time and physical infirmities began to take their toll.

His public activities were not limited to medical affairs. He was president of Temple Beth-El for over a generation, a founder and director of the Hudson County Hebrew Home for Orphans and Aged, a past president and treasurer of District Grand Lodge No. 3 B'nai B'rith, a life member of the Jersey City Lodge of Elks, a Mason, a member of the Advisory Board of the Salvation Army, director of the Jewish Community Center of Jersey City, and a member of the Advisory Board of Selective Service in World War II.

Throughout his life he fulfilled the highest ideals of citizenship and of the medical profession. He was a firm believer in the brotherhood of man and the Fatherhood of God without distinction as to race, color or creed.

With the death of Dr. Berthold S. Pollak on June 27, there came to an end an era in medicine and public health, especially in tuberculosis, not only in Hudson County but throughout the State. His passing leaves a keen sense of loss in the hearts of his colleagues, co-workers, patients, and all who knew him.

ABRAHAM E. JAFFIN, M.D., F.A.C.P.

DR. E. ROLAND SNADER, JR.

Dr. Snader was a distinguished physician who has left a lasting mark among his confreres.

Dr. Snader was born in Philadelphia, November 1, 1895. He obtained his B.S. degree at Haverford College and M.D. degree at Hahnemann Medical College of Philadelphia in 1921.

He served in various capacities at Hahnemann and was thought of as a brilliant teacher and a friend of the students. He was Chief Medical Resident, Clinical Assistant, Electrocardiographer, Assistant Physician and Physician at Hahnemann Hospital; Professor of Clinical Medicine in Hahnemann Medical College and Hospital of Philadelphia.

Dr. Snader also was consulting Physician in Internal Medicine at the Allentown State Hospital, the William McKinley Memorial Hospital, Trenton, N. J., the Homeopathic Hospital of Chester County, West Chester, and the J. Lewis Crozer Home for Incurables and Homeopathic Hospital in Chester.

Dr. Snader was Past President of the Homeopathic Medical Society of the County of Philadelphia, and a Past Trustee of the Homeopathic Medical Society of the State of Pennsylvania. He was an interested and diligent worker on the Council of the American Diabetes Association. He was a member of the Philadelphia Medical Club and became a Fellow of the American College of Physicians in 1928. He was a Diplomate of the American Board of Internal Medicine. Dr. Snader is the author of numerous medical papers.

Dr. E. Roland Snader was a forthright, vigorous, jolly, vital gentleman. He was intolerant of all insincerity. He was implicitly trusted by his colleagues and patients, and warmly loved by his many friends.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania